University of Alberta

Meningitis in preterm infants from Northern and Central Alberta

by

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To my parents

ABSTRACT

This study was undertaken to determine if meningitis in premature neonates is associated with adverse sequelae in early childhood.

Using a hospital-based inception cohort design for infants ≤ 36 weeks gestation as well as a nested case control design for infants < 1250g, premature infants with meningitis were shown to be at an increased risk of mortality and poor neurodevelopmental outcome. Post-meningitis hydrocephalus requiring ventriculoperitoneal shunting was a common complication and an important prognostic variable for adverse neurodevelopmental outcome and cognitive ability.

Meningitis in preterm infants is predominantly a nosocomial infection with coagulase-negative staphylococcus the pathogen most commonly isolated. This study confirms the importance of performing a lumbar puncture in any premature infant with suspected late-onset sepsis.

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List of Abbreviations

Abbreviation	Meaning
BSID-II	Bayley Scales of Infant Development II
BW	birth weight
CLD	chronic lung diseaes
CNS	central nervous system
CONS	coagulase-negative staphylococci
CSF	cerebrospinal fluid
CT	computed tomography
EEG	electroencephalogram
EOM	early onset meningitis
GA	gestational age
GBS	group B Streptococcus or *Streptococcus agalactiae*
IUGR	intrauterine growth restriction
IVH	intraventricular hemorrhage
LBW	low birth weight (i.e. < 2500)
LOM	late onset meningitis
LOS	length of stay
LP	lumbar puncture
MDI	Mental Development Index
MRI	Magnetic Resonance Imaging
NEC	necrotising enterocolitis
NICU	Neonatal Intensive Care Unit

PDA	patent ductus arteriosus
PDI	Psychomotor development index
PHH	Post hemorrhagic hydrocephalus
PVL	periventricular leukomalacia
RAH	Royal Alexandra Hospital
RBC	red blood cell count
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SCH	Stollery Children's Hospital
SD	standard deviation
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
spp	species
VLBW	very low birth weight (i.e. < 1500g)
VP	ventriculoperitoneal
WCC	white cell count

Chapter 1

Introduction and literature review

Section 1.1: Introduction and statement of the problem

Meningitis is a rare but serious disease occurring more commonly during the neonatal period than at any other time of life (Klein, Feigin et al. 1986; de Louvois 1994; Volpe 2000). Furthermore, premature infants are more likely to develop meningitis than are term infants (Volpe 2000; Klein 2001). As advances in neonatal intensive care have improved the survival of preterm infants, in particular very low birth weight infants (VLBW) [birth weight <1500g], the incidence of nosocomial infections, including meningitis, has increased (Doctor, Newman et al. 2001). Rates of infection increase with decreasing gestational age and birth weight, thus the most premature infants are at the highest risk of developing meningitis, predisposing this already vulnerable population to further risk of neonatal complications, prolonged hospitalization, long term morbidity and death (Stoll, Gordon et al. 1996; Stoll, Hansen et al. 2002).

The epidemiology of meningitis, responsible pathogens, host responses to infection and outcomes are unique in the neonatal period (Volpe 2000; Polin and Harris 2001). The mortality and morbidity associated with neonatal meningitis remains high (Overall 1970; Fitzhardinge, Kazemi et al. 1974; Franco, Cornelius et al. 1992; Klinger, Chin et al. 2000; Bedford, de Louvois et al. 2001; Stevens, Eames et al. 2003). Prognosis appears worse in VLBW infants (Bortolussi, Krishnan et al. 1978; Perlman, Rollins et al. 1992; Doctor, Newman et al. 2001), a group of children already at high risk of death and disability (Robertson, Sauve et al. 1994; Hack and Fanaroff 2000; Vohr, Wright et al. 2000; Hack, Flannery et al. 2002). Because there is little specific information available

on meningitis in premature neonates (Perlman, Rollins et al. 1992; Doctor, Newman et al. 2001), the long-term prognosis of individual patients is often based on extrapolation from outcomes in term infants and older children (Fitzhardinge, Kazemi et al. 1974; Franco, Cornelius et al. 1992; Klinger, Chin et al. 2000; Stevens, Eames et al. 2003).

The main objective of this study is to elucidate whether the outcomes (survival and long term neurodevelopment) of infants with birth weight < 1250 grams are worsened if they develop meningitis. This study also describes the incidence of meningitis, clinical features, diagnosis and interpretation of cerebrospinal fluid (CSF) values, distribution of infecting pathogens, risk factors for disease and the impact of infection on subsequent hospital course, mortality and neurodevelopmental outcomes of all premature newborns from northern and central Alberta who had meningitis at the tertiary level neonatal intensive care units (NICUs) in Edmonton over the last decade. With regionalization of perinatal care, all high-risk premature deliveries and neonates, including those with birth weight < 1250g, are referred to the tertiary care obstetric and neonatal units in Edmonton. Infants at risk of neurodevelopmental sequelae, which includes all infants < 1250g and those diagnosed in the NICU with meningitis, are referred to the Neonatal and Infant Follow-up Clinic at the Glenrose Rehabilitation Hospital where they are assessed by a multidisciplinary team knowledgeable in neonatal follow-up.

Through these observations, we hope to aid clinicians in better defining the risk factors, diagnostic features and clinical course of meningitis in preterm infants. Further, we hope to be able to provide a rationale for parental counseling about the prognosis for their child in an early phase of the disease.

Section 1.2: Literature review of neonatal meningitis

More involved than just the meninges (Swartz 1984)

Before the advent of sulfonamides and other antibiotic agents, meningitis in the neonate was, with rare exceptions, a fatal disease (Nyhan and Richardson 1963). Accounts of conditions causing delirium, including meningitis, were described by Socrates and Galen, but the term 'meningitis' was first used by Herpin in 1903 (de Louvois 1994). Discovery of the utility of the lumbar puncture by Quincke in 1891 aided diagnosis while the patient was still alive (Quincke 1891). Development of equine antimeningococcal antiserum by Flexner was the first therapy used in altering the course of meningitis (Flexner 1913). Since then, the prognosis of adult and childhood meningitis has dramatically improved with the use of antimicrobial agents and preventative strategies, specifically vaccinations (Schuchat, Robinson et al. 1997; Lingappa, Rosenstein et al. 2001; Whitney, Farley et al. 2003; Swartz 2004).

Macaigne published the first report of meningitis in the newborn in 1892 (Barrett, Rammelkamp et al. 1942). Unlike in older children and adults, concerns regarding the difficulty in diagnosis, the organisms (which are often not traditionally pathogenic), the immune response of the host, the high fatality and the long term morbidity seen in this newborn population continue today despite advances in neonatal care (Nyhan and Richardson 1963).

1.2.1: Epidemiology

Meningitis in the neonate is usually a sequela of septicemia. The clinical manifestations of these two syndromes may be indistinguishable. The incidence of sepsis and meningitis varies from centre to centre (Hristeva, Booy et al. 1993; Moreno, Vargas

et al. 1994; Gebremariam 1998; Holt, Halket et al. 2001; Grupo 2002; Persson, Trollfors et al. 2002; Laving, Musoke et al. 2003; May, Daley et al. 2005; Vergnano, Sharland et al. 2005), but have been reported at 0.6 - 5.2 per 1000 live births and 0.3 - 0.5 per 1000 live births for all neonates for sepsis and meningitis respectively (Klein 2001; Philip 2003). In low birth weight infants [BW < 2500g], the incidence of sepsis and meningitis is higher, 4.3 - 40 per 1000 live births and 1.4 - 2.8 per 1000 live births for sepsis and meningitis respectively (Klein 2001; Philip 2003). Neonatal meningitis on the whole occurs as single sporadic cases; outbreaks are rare and are usually due to nosocomial spread (de Louvois 1994).

The types of pathogens causing sepsis and meningitis in the newborn have changed considerably over the last 50 years, particularly in VLBW infants managed in the NICU (de Louvois 1994; Volpe 2000; Klein 2001; Polin and Harris 2001; Stoll, Hansen et al. 2002; Stoll, Hansen et al. 2002; Philip 2003). Early reports identified enteric gram negative bacilli, particularly *Escherichia coli*, as the most frequent causative organism (Overall 1970; Bortolussi, Krishnan et al. 1978; de Louvois 1994). One of the first accounts of neonatal meningitis caused by group B streptococcus (GBS) was by Nyhan and Fousek in the 1950's (Nyhan and Fousek 1958). There was an increasing incidence of sepsis and meningitis caused by GBS in the mid-to late 1970's; GBS infection appears to be waning with prenatal GBS screening and the use of maternal intrapartum antibiotics (Synnott, Morse et al. 1994; Schrag, Gorwitz et al. 2002; Schrag, Zell et al. 2002; Stoll, Hansen et al. 2002; May, Daley et al. 2005). Staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis*, have been recognized as causes of meningitis particularly as nosocomial infections in patients with indwelling

central catheters and intraventricular devices such as reservoirs or shunts (Volpe 2000; Klein 2001; Persson, Trollfors et al. 2002; Stoll, Hansen et al. 2002). As *S. epidermidis* (the most common type of coagulase-negative staphylococcus) is a normal commensal present on the skin, isolation of this organism from cultures of blood or CSF may represent contamination. The clinical picture, repeat culture of blood and other laboratory investigations assist in differentiating contamination from true invasion.

The remaining pathogens are accounted for principally by other streptococcal and staphylococcal species, other gram-negative enteric bacilli, and a variety of unusual organisms (Volpe 2000; Klein 2001). *Listeria* serotype IVb has been implicated in the majority of cases of meningitis caused by *Listeria monocytogenes* (Polin and Harris 2001). *Candida albicans*, particularly in the sick premature infant, can cause disseminated infection with meningitis and intracranial microabscesses (Lee, Cheung et al. 1998; Volpe 2000; Klein 2001).

Two patterns of sepsis - 'early-onset' and 'late-onset'- can be distinguished (Klein 2001). In early-onset disease, i.e. onset within the first 48 hours after birth, infection appears to be derived perinatally from a colonized or infected birth canal, thus associated obstetrical complications (e.g., premature rupture of maternal membranes, premature onset of labour, chorioamnionitis, peripartum maternal fever) and premature birth are common. In late onset disease, i.e. onset after the first few days after birth, particularly in VLBW infants, infection is often acquired nosocomially secondary to sepsis associated with necrotizing enterocolitis, indwelling catheters, parenteral hyperalimentation and contaminated equipment. Because different microorganisms are responsible for the two forms of disease, the choice of antimicrobial agents also differs. Meningitis due to GBS

is usually associated with late-onset infection when it is most frequently associated with GBS serotype III. Some organisms, such as *E. coli*, groups A and B streptococci, and *L. monocytogenes*, may be responsible for both early-and late-onset disease, whereas others, such as *S. aureus*, coagulase-negative staphylococcus (CONS), and *Pseudomonas aeruginosa*, are associated almost exclusively with late-onset disease.

1.2.2: Risk factors for neonatal meningitis

There are a number of predisposing factors, either alone or in combination, that are associated with neonatal meningitis, thus any approach to decreasing the morbidity and mortality of neonatal meningitis must be multifaceted. Risk factors that have been associated with neonatal meningitis can be categorized as follows (de Louvois 1994; Volpe 2000):

a) Factors related to pregnancy and delivery

The intrauterine environment is normally sterile primarily because amniotic fluid has bactericidal properties. Complications of labour and delivery such as obstetrical trauma, maternal peripartum infection and chorioamnionitis, and premature and/or prolonged rupture of membranes may predispose to sepsis and meningitis (Overall 1970; de Louvois 1994). Early-onset sepsis, which almost always occurs in the first 24 hours after birth, is often associated with these complications, suggesting that infection occurs *in utero* or at the time of delivery (Klein 2001).

b) Factors related to the infant

Low birth weight is the factor most significantly associated with meningitis (de Louvois 1994; Fanaroff, Korones et al. 1998; Klein 2001). The rate of infection is inversely related to gestational age and birth weight (Fanaroff, Korones et al. 1998; Stoll,

Hansen et al. 2002). Male infants seem to be more susceptible to infection (Stevenson, Verter et al. 2000; Klein 2001). Twins are also more susceptible to meningitis, which may be related to preterm labour and low birth weight (Klein 2001). Independent of gestational age and birth weight, both mono-and dichorionic twins are at higher risk of early- and late-onset sepsis (Klein 2001), particularly GBS sepsis (Pass, Khare et al. 1980; Edwards, Jackson et al. 1981). Deficiencies in non-specific immunity (granulocytic leukocytes and opsonins) and specific immunity (T- and B-lymphocyte-antibody system, complement and lysozyme) are described in neonates, in particular in premature neonates (de Louvois 1994; Fanaroff, Korones et al. 1998; Volpe 2000). In addition, the premature infant is deprived of a full supply of passively transferred maternal antibody.

Another group of infants at high risk of meningitis are those with congenital malformations of the central nervous system such as neural tube defects. This thesis will not focus on these patients, nor include them in the sample population.

c) Factors related to the neonatal environment

Any disruption of the protective capability of the intact skin or mucosa may be associated with infection. In NICU patients, prolonged need for intubation and mechanical ventilation, presence of peripheral and central venous and arterial catheters, presence of a ventricular reservoir or a ventriculoperitoneal (VP) shunt, skin breakages for venipuncture, exposure to nursery personnel, parents or other infants harbouring pathogenic organisms predispose to late-onset sepsis and meningitis (Klein 2001; Stoll, Hansen et al. 2002).

d) Factors related to the microorganism

The relative importance of bacterial virulence and impaired host defense interact in the development of invasive infection in the newborn. There are specific serotypes of organisms, however, which have a higher propensity to meningeal involvement: serotype III of GBS, K_1 strains of *E. coli* and serotype IVb of *L. monocytogenes* (de Louvois 1994; Klein 2001).

1.2.3: Pathogenesis

The leptomeninges consist of two membranes: the pia mater (applied to the brain and spinal cord) and the arachnoid (just inside the dura and ensheathing the cranial and spinal nerves). Bacteria gain access to the brain through the bloodstream to the choroid plexus (choroid plexitis), with subsequent entrance of bacteria into the ventricular system (ventriculitis), and then involvement of the arachnoid via normal CSF flow (arachnoiditis) (Swartz 1984; Klein 2001).

Although the leptomeninges and the CSF in the subarachnoid space are the primary sites of infection in meningitis, pathologic changes are not confined to these areas. The most consistent findings at autopsy are purulent exudates of the meninges and of the ependymal surfaces of the ventricles associated with vascular inflammation (Volpe 2000; Philip 2003). Other neuropathological features of meningitis are classified into acute (arachnoiditis, ventriculitis, vasculitis, cerebral edema, infarction, encephalopathy) (Bortolussi, Krishnan et al. 1978) and chronic (hydrocephalus, multicystic encephalomalacia-porencephaly, cerebral cortical and white matter atrophy, cerebral cortical developmental defects) (Perlman, Rollins et al. 1992; Volpe 2000; Philip 2003).

The brain injury seen in neonatal bacterial meningitis is caused by a complex series of mechanisms including increased permeability of the blood-brain barrier, inflammatory response by cytokines, generation of free radicals, and impaired cerebral blood flow and autoregulation. The interaction of these effects leads to diffuse neuronal injury, periventricular leukomalacia, and thrombotic cerebral infarction (Volpe 2000; Shah, Daley et al. 2005).

1.2.4: Clinical manifestations

Clinical signs of meningitis in neonates can be subtle and non-specific and include lethargy, hypotonia, irritability, seizures, feeding intolerance, temperature instability, respiratory distress, apnea, jaundice, hypotension, and hypo-or hyperglycemia. A bulging fontanelle may be a late sign of meningitis. Neck stiffness (or meningismus), Kernig and Brudzinski signs are rarely detected in preterm infants (Volpe 2000; Philip 2003).

With early-onset meningitis, the clinical presentation is often dominated by signs of sepsis and respiratory distress rather than neurological manifestations. The course is usually fulminating with multisystem involvement and high associated mortality. In late onset disease, meningitis is the dominant manifestation, but other non-neurological signs such as temperature instability and feeding intolerance are often present as well. The course is not as fulminating and mortality rates are usually lower than with early-onset disease (Klein 2001).

Major neurological complications of meningitis include (Volpe 2000):

(1) Increased intracranial pressure caused by cerebral edema (vasogenic and cytotoxic), acute hydrocephalus and intracerebral mass or extraparenchymal collection;

(2) Ventriculitis causing difficulty in eradication of infection;

(3) Acute hydrocephalus from closure of the aqueduct or the foramina of the fourth ventricle by purulent exudates (ventriculitis), or through inflammatory impairment of CSF resorption through the arachnoid channels (arachnoiditis);

(4) Intracerebral mass or extraparenchymal collection, e.g., abscess, subdural effusion, particularly common with *Citrobacter diversus, Serratia marcescens,* or *Proteus* species which characteristically cause a hemorrhagic meningoencephalitis with intense bacterial infiltration of cerebral vessels and surrounding tissues;

(5) Hemorrhage, venous thrombosis and cerebral infarction related to vascular (both venous and arterial) involvement;

(6) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

1.2.5: Diagnosis

The importance of performing a lumbar puncture (LP) as part of the diagnostic evaluation of a neonate, term and preterm, with suspected sepsis has been the subject of debate (Visser and Hall 1980; Eldadah, Frenkel et al. 1987; Hendricks-Munoz and Shapiro 1990; MacMahon, Jewes et al. 1990; Schwersenski, McIntyre et al. 1991; Hristeva, Booy et al. 1993; Kumar, Sarkar et al. 1995; McIntyre and Isaacs 1995; Wiswell, Baumgart et al. 1995; Johnson, Whitwell et al. 1997; Stoll, Hansen et al. 2004). In the first week after birth, the yield from "routine" CSF evaluation is low even in infants at high risk for sepsis (Eldadah, Frenkel et al. 1987; Hendricks-Munoz and Shapiro 1990; Hristeva, Booy et al. 1993; Johnson, Whitwell et al. 1997). This is complicated by the frequent use of maternal intrapartum antibiotics for GBS and other infectious risk factors, and the fear of missing or delaying the diagnosis of meningitis

(Wiswell, Baumgart et al. 1995). After the first week of life, the incidence of meningitis increases, and therefore an LP is indicated in every neonate, especially VLBW infants, evaluated for sepsis (Visser and Hall 1980). Up to one third of infants with positive CSF cultures will have concurrent negative blood cultures, further emphasizing the need to include an LP as part of the evaluation for sepsis (Visser and Hall 1980; Stoll, Hansen et al. 2004).

Diagnosis of meningitis is based on evidence of inflammation of the meninges as indicated by an elevated number of white blood cells in CSF with predominantly polymorphonuclear leukocytes, elevated protein concentration, depressed glucose concentration relative to blood glucose concentration and culture of a pathogen in CSF, which ideally should be obtained prior to the initiation of antibiotic therapy. Culture of CSF remains the "gold standard" for the diagnosis of meningitis in the neonate.

Examination of CSF microscopically by Gram stain may reveal the presence of an organism before culture results are available. It is also possible to detect bacterial antigen in CSF using countercurrent immunoelectrophoresis or latex particle agglutination, particularly for organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, and GBS (Klein 2001; Polin and Harris 2001), but these procedures are not routinely performed because of limited sensitivity and specificity (Baker, Webb et al. 1980; Webb and Baker 1980; Webb, Edwards et al. 1980; Hoban, Witwicki et al. 1985). .

Interpretation of CSF culture, chemistry and cell counts in the newborn can however be difficult (Volpe 2000; Klein 2001):

a) Lumbar puncture may be more difficult to perform especially in neonates with cardiorespiratory compromise and may thus need to be delayed until the infant is more stable after initiation of antibiotics. However, even days after the start of antimicrobial therapy, cytologic tests and CSF chemistry should identify the presence of an inflammatory reaction.

b) Because of intracranial bleeds (Volpe 2000) and traumatic taps, "bloody" taps are more frequently encountered in neonates. These make interpretation of CSF parameters difficult and can result in false-positive CSF cultures in a bacteremic infant.

c) There is uncertainty regarding normal CSF values in preterm infants. Firstly, the cell content and chemistry of the CSF of newborns differs from that of older children and adults; furthermore, the values vary in preterm and term newborns and also over the first few weeks after birth (Rodriguez, Kaplan et al. 1990; Remington and Klein 2001). Secondly, there is a large overlap between values found in the normal newborn and those found in newborns with culture-proven meningitis (Sarff, Platt et al. 1976; Gruskay, Harris et al. 1989; Remington and Klein 2001). For instance, CSF values of protein and glucose are higher in premature infants which may reflect increased permeability of the blood-brain barrier.

d) Clinically important bacteremia and meningitis need to be distinguished from contamination when organisms that are part of the normal skin flora (diptheroids, coagulase-negative staphylococci, *Bacillus* species, or nonhemolytic streptococci) are identified on culture (Klein 2001).

Neuroimaging studies are useful aids in the diagnosis and assessment of complications of meningitis. The most useful and accessible technique for imaging the brain in neonates is ultrasonographic imaging at the bedside through the anterior fontanel (Perlman, Rollins et al. 1992; Volpe 2000). Acutely, ultrasound may reveal evidence of ventriculitis (intraventricular strands attached to the ventricular surface and echogenic ependyma), ventriculomegaly, periventricular or focal cerebral parenchymal echogenicities, and extracellular fluid collections. Chronic changes such as hydrocephalus and multicystic parenchymal change can also be detected by cranial ultrasound. The value of this modality of imaging is that serial studies can be done easily to define progression of potential complications. In a case series of late onset meningitis in VLBW infants, sonographic abnormalities associated with meningitis included new development or progression of periventricular-intraventricular hemorrhage, progressive ventriculomegaly, thalamic echodensities, and intraventricular strands attached to the ventricular walls (Perlman, Rollins et al. 1992). Computed tomography (CT) scan in the acute stages of meningitis may show cerebral edema, ventriculomegaly, infarction, abscess or subdural collection. Subsequently, CT scan is useful in showing hydrocephalus, multicystic encephalomalacia, and cerebral cortical and white matter atrophy. Magnetic resonance imaging (MRI) is increasingly being used in premature neonates to diagnose sequelae of meningitis, particularly early detection of cerebral white matter injury (Blaser, Jay et al. 2002; Shah, Daley et al. 2005).

1.2.6: Treatment and management

Prompt initiation of antimicrobial therapy is the mainstay of treatment of neonatal meningitis in light of the rapid progression of disease and high mortality and morbidity

(de Louvois 1994; Klein 2001). In the first week after birth, ampicillin and an aminoglycoside (usually gentamicin) are effective for the most common etiologic bacteria causing early-onset meningitis. For suspected late-onset meningitis, empiric therapy usually involves vancomycin (to cover for hospital-acquired staphylococcal infection) and a third generation cephalosporin (usually cefotaxime). Once the pathogen has been identified and the antibiotic susceptibility results are available, the single drug or combination of drugs that is most effective is used. There is no precise or proven method to determine the duration of antibiotic therapy. Useful guides include the infant's clinical course, the etiologic organism and timing of sterilization of the CSF.

Other adjunctive measures may also be important in determining survival and minimizing long-term sequelae. Supportive measures such as assisted ventilation, cardiovascular support with fluids and pressor agents, and treatment of seizures are often required. Acute hydrocephalus with elevated intracranial pressure may require ventricular drainage (external ventricular drain acutely and ventricular reservoir once the organism is cleared). A ventriculoperitoneal shunt may be required for longer-term management of the hydrocephalic state. There is no evidence to support the use of corticosteroids in neonatal meningitis, particularly in preterm infants because of concerns with increased risk of sepsis and long term sequelae secondary to postnatal steroid exposure (Stoll, Temprosa et al. 1999; Barrington 2001; 2002; Yeh, Lin et al. 2004). Intrathecal and intraventricular gentamicin provide no additional benefit over intravenous antibiotics, and in fact may cause harm (McCracken and Mize 1976).

Preventative strategies are non-specific and have not had a major impact on the incidence of meningitis in preterm infants, unlike in older children where immunization

for pneumococcus, meningococcus and *H. influenzae* has been very effective. Improvements in the health of pregnant woman and access to prenatal care, regionalization of high-risk obstetric and neonatal intensive care expertise, careful hand washing, fastidious management of central intravascular catheters, infection control measures, surveillance systems within the hospital and quality improvement initiatives have contributed to enhanced outcomes for premature newborns (Horbar, Rogowski et al. 2001; Klein 2001; Aly, Herson et al. 2005). The use of maternal chemoprophylaxis for prevention of early onset GBS sepsis in neonates has led to a marked decrease in the incidence of early-onset GBS infection in neonates, but only 6% with early onset GBS had meningitis (Schrag, Zywicki et al. 2000). Maternal immunoprophylaxis against GBS with a vaccine has shown some promise, but has drawbacks such as disappointing immunogenic responses in women exposed to the polysaccharide vaccine and poor transfer of antibody to infants born < 32 weeks, the group of infants at highest risk of developing meningitis (Baker, Rench et al. 1988; Baker, Rench et al. 1990).

1.2.7: Outcome and prognosis

Until recently, the case fatality rate of neonatal meningitis has remained high. In the 1950's and 1960's, the case fatality associated with neonatal meningitis was 60% or more (Ziai and Haggerty 1958; Groover, Sutherland et al. 1961; Yu and Grauaug 1963; Berman and Banker 1966; Franco, Cornelius et al. 1992). More recently, in the Netherlands (1976–82), the case fatality rate amongst 280 cases was 27% (Mulder and Zanen 1984), in Australia (1987-1989), the rate amongst 116 cases was 26% (Francis and Gilbert 1992), and in England and Wales (1985-1987), the rate amongst 450 cases was 20% (de Louvois, Blackbourn et al. 1991). Even more recently, from Canada, the case

fatality rate had improved to 13% in 101 neonates with bacterial meningitis (Klinger, Chin et al. 2000) and to 6.6% in 274 neonates in England and Wales (Harvey, Holt et al. 1999; Holt, Halket et al. 2001).

Concern has been raised that improved survival after neonatal meningitis has been at the expense of major neurological sequelae (Lewis and Gupta 1977). Amongst survivors, major neurological sequelae including cerebral palsy, seizure disorder, mental retardation, hydrocephalus, sensorineural hearing loss, optic atrophy with decreased visual acuity, endocrine abnormalities, behavioural disorders and spinal cord dysfunction have been described (Moffett and Berkowitz 1997; Klinger, Chin et al. 2000; Volpe 2000; Bedford, de Louvois et al. 2001; Klinger, Chin et al. 2001; Grupo 2002; Philip 2003). Of all the pathogens, long-term outcomes are most frequently reported for GBS meningitis where poorer outcomes with combined mortality and morbidity approximately 50% (Horn, Zimmerman et al. 1974; Edwards, Rench et al. 1985), as well as more encouraging outcomes with morbidity approximately 15% (Chin and Fitzhardinge 1985; Wald, Bergman et al. 1986) have been reported. These reports on GBS meningitis describe children who developed meningitis in the 1960's to the 1980's, the majority of whom were term gestation.

The specific consequences of meningitis amongst premature infants [$\leq$36 weeks gestational age] or VLBW infants [BW < 2500g] have been less well documented. Amongst VLBW preterm infants, neonatal sepsis itself (with or without meningitis) has been associated with cerebral white matter damage and cerebral palsy (Faix and Donn 1985; Msall, Buck et al. 1994; Murphy, Hope et al. 1997; Wheater and Rennie 2000). Sepsis and meningitis have been shown to be predictors of major neurosensory

abnormality and subnormal mental developmental index (<70) in infants with birth weight < 1000g (Hack, Wilson-Costello et al. 2000). In a large cohort of approximately 6000 extremely low birth weight infants (ELBW) [BW < 1000g], neonatal infection (clinical infection, sepsis, sepsis and necrotizing enterocolitis, and meningitis with or without sepsis) was associated with adverse neurodevelopmental and growth outcomes at 18-22 months adjusted age, including cerebral palsy, low Bayley Scales of Infant Development II (Bayley 1993) on the mental development index (MDI) and psychomotor development index (PDI), vision impairment, and impaired head growth (Stoll, Hansen et al. 2004). In a case-control study of 111 term and preterm neonates with meningitis and 113 controls from both birth hospital and community practices in England and Wales, cases of lower birth weight had a higher incidence of poor outcome (cerebral palsy, IQ < 70, global delay, special education, sensorineural hearing loss): 12% in infants > 2500g, 31% in infants 1500-2499g and 44% in infants < 1500g (Stevens, Eames et al. 2003). In the only study currently in the literature focusing on meningitis in VLBW infants and their long term outcomes, 64 infants diagnosed with meningitis (1977-1995) were compared to 3398 VLBW infants admitted to the same NICU during the same period who did not have meningitis. Survivors of neonatal meningitis were shown to have more major neurologic abnormality (41% vs. 11%) and subnormal (<70) MDI on the Bayley Scales of Infant Development (BSID) (38% vs. 14%) even after controlling for risk factors such as birth weight (BW), intraventricular hemorrhage (IVH), chronic lung disease (CLD) and social factors (Hack, Wilson-Costello et al. 2000; Doctor, Newman et al. 2001). Although this study provides useful information, the infants who developed meningitis had lower GA and BW in comparison to infants who did not develop

meningitis. Also, infants with meningitis had a higher incidence of neonatal complications such as respiratory distress syndrome (RDS), sepsis, necrotizing enterocolitis (NEC), chronic lung disease (CLD), periventricular hemorrhage, periventricular leukomalacia (PVL) and hydrocephalus. It is thus difficult to ascertain the effects of meningitis on the neurologic and developmental outcomes of these VLBW infants in the presence of these confounding factors.

Certain factors may have prognostic significance for fatal outcome or survival with neurological sequelae. The mortality associated with gram negative bacillary meningitis is usually higher than that with other organisms, exceeding 30% in most series (Fitzhardinge, Kazemi et al. 1974; Franco, Cornelius et al. 1992; Unhanand, Mustafa et al. 1993; de Louvois 1994), and appears to be worsened by early-onset disease (Mulder, van Alphen et al. 1984; May, Daley et al. 2005). Long term neurodevelopmental outcomes are also somewhat worse with gram negative bacillary meningitis with approximately 60% having residual neurological deficits (Franco, Cornelius et al. 1992; Unhanand, Mustafa et al. 1993). The association with infecting organism is not however borne out in all studies with no difference in outcome between GBS and gram negative cases (Stevens, Eames et al. 2003). Most studies include term infants, but in those studies describing outcomes for both term and preterm infants, low birth weight [BW < 2500g] is often cited as a poor prognostic indicator when associated with meningitis (Overall 1970; Bortolussi, Krishnan et al. 1978; Franco, Cornelius et al. 1992; Stevens, Eames et al. 2003; May, Daley et al. 2005). Other poor prognostic factors in neonatal meningitis include the presence of coma, semicoma or seizures at the time of presentation, duration of seizures > 72 hours, decreased perfusion, use of inotropes to

maintain blood pressure, leukopenia [total peripheral WBC count < 5.0 x 10^9/l] or neutropenia [absolute neutrophil count < 1.0 x 10^9/l], markedly elevated CSF protein content [CSF protein >3g/l], gram negative bacillary meningitis, degree of background abnormality on electroencephalogram (EEG), elevated endotoxin and interleukin-1 concentrations in CSF, (Overall 1970; Fitzhardinge, Kazemi et al. 1974; Bortolussi, Krishnan et al. 1978; Edwards, Rench et al. 1985; McCracken, Mustafa et al. 1989; Perlman, Rollins et al. 1992; Unhanand, Mustafa et al. 1993; Klinger, Chin et al. 2000; Holt, Halket et al. 2001; Klinger, Chin et al. 2001). The prognosis of meningitis with associated brain abscesses in the neonate is guarded (Renier, Flandin et al. 1988).

Although these prognostic factors may be useful, the outcome in neonatal meningitis is likely dependent upon the interplay of many factors and prognostic judgments should be carefully individualized. Various authors suggest that a cautiously optimistic note may be struck with parents when discussing the long term implications of neonatal meningitis as in no other neonatal neurological disease is dramatic recovery from a potentially devastating clinical state more likely to be observed than in an infant with neonatal meningitis (Klein, Feigin et al. 1986; Volpe 2000; Philip 2003).

1.2.8: Summary

Meningitis in the preterm infant presents unique dilemmas to families and to clinicians. Although the case fatality rate of neonatal meningitis has improved, neurodevelopmental morbidity (cerebral palsy, cognitive delay, seizure disorder, hydrocephalus, sensorineural hearing loss, visual impairment and poor growth) remains a major concern. Of all age groups, the incidence of meningitis is highest in low birth weight newborns. Strategies to prevent the onset of neonatal meningitis have had little

impact. Difficulties with diagnosis (clinical manifestations, technical difficulties of performing a lumbar puncture, CSF findings and interpretation, and the organisms involved) also present challenges in preterm infants.

This study aims to describe the clinical course and outcomes of premature newborns from northern and central Alberta who had meningitis at the tertiary level NICUs in Edmonton over the last decade. Through these observations, we hope to aid clinicians in better defining the risk factors, diagnostic features and clinical course of meningitis in preterm infants. Further, we hope to be able to provide a rationale for parental counseling about the prognosis for their child in an early phase of the disease.

Section 1.3: Objectives and hypothesis

1.3.1: Primary objective and hypothesis

The **primary objective** of this study is to elucidate the outcomes (survival and long-term neurodevelopment) of infants with meningitis with birth weight < 1250 grams in comparison to infants without meningitis.

The main hypothesis is that neonates with birth weight < 1250 grams who develop meningitis in the NICU fare worse in survival and long-term neurodevelopmental outcomes than those without meningitis.

1.3.2: Secondary objectives

For this study, all premature infants [gestational age ≤ 36 weeks] who were diagnosed with meningitis in the NICU were identified. A subgroup of this cohort, infants < 1250g with meningitis, were further selected and compared to infants < 1250g without meningitis. Two comparisons were undertaken to achieve the following objectives.

1.3.2.1: Related to infants < 1250g:

1. To document the incidence of meningitis in infants < 1250g in a hospital-based, tertiary NICU setting in Edmonton
2. To determine clinical and risk characteristics for meningitis
3. To elucidate outcomes, survival and neurodevelopmental sequelae at 18–months adjusted age between infants with and without meningitis
4. To ascertain any prognostic factors influencing mortality and morbidity
5. To ascertain any prognostic factors influencing the Mental Developmental Index, an indicator of cognitive ability, at 18-months adjusted age

1.3.2.2: Related to all infants ≤ 36 weeks

This comparison includes all infants ≤ 36 weeks with meningitis and assesses these infants according to preset criteria for diagnosing definite and possible meningitis:

1. To describe clinical characteristics of definite and possible meningitis including presenting manifestations, infecting pathogen, and laboratory findings
2. To elucidate outcomes, survival and neurodevelopmental sequelae at 18–months adjusted age between infants with definite and possible meningitis
3. To ascertain any prognostic factors influencing mortality and morbidity amongst all infants ≤ 36 weeks with meningitis in the NICU.

Chapter 2

Methods

Section 2.1: Study design and participants

2.1.1: Study design

This is a hospital-based, inception cohort study of preterm newborns with gestational age ≤ 36 weeks who were admitted to the Northern Alberta Neonatal Intensive Care Program over a 14-year study period, January 1990 to December 2003. Infants who developed meningitis during the neonatal period [the first 28 days after birth, or during their NICU stay] were identified. Two comparisons were undertaken (FIGURE 2.1):

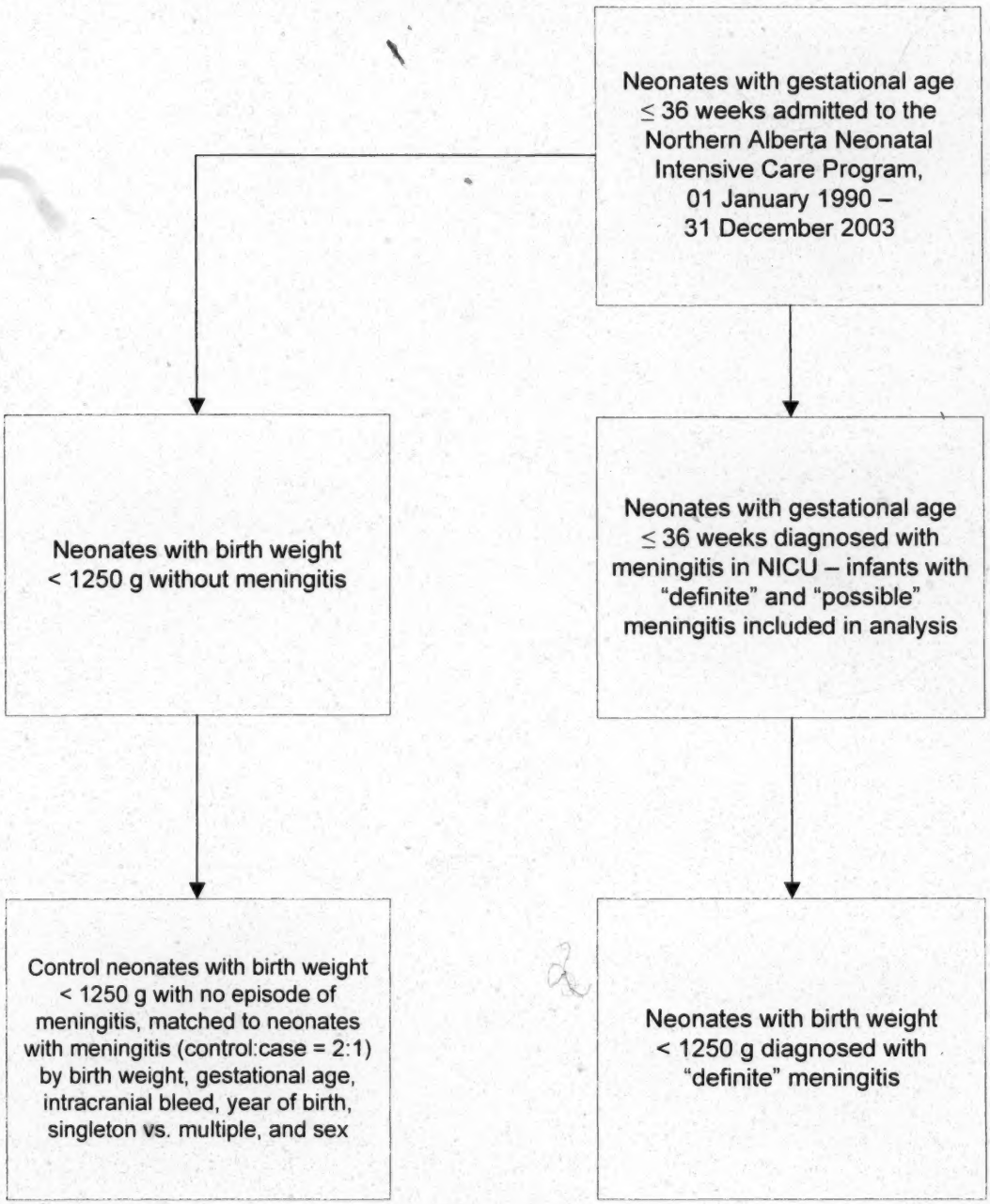
1. During the study period, all liveborn neonates from northern and central Alberta with birth weight < 1250g were admitted to the tertiary care NICUs in Edmonton. The number of infants < 1250g with meningitis was determined using criteria as defined below. The incidence of meningitis amongst infants < 1250g admitted to the Northern Alberta Neonatal Intensive Care Program could thus be calculated. After chart review, the case fatality rate from meningitis could also be determined. (Not all infants ≤36 weeks gestation are admitted to the tertiary NICUs, thus the incidence of meningitis in the whole cohort of preterm infants could not be calculated.)

   From the cohort of all preterm infants ≤36 weeks gestation with meningitis, infants with birth weight < 1250g with definite meningitis were further identified. These infants were matched to control infants without meningitis. In this nested case control study, risk characteristics for meningitis are

determined. Cases and controls were followed to 18-months adjusted age. Outcomes between the groups are compared and prognostic variables for outcomes and cognitive ability are ascertained. (See Section 1.3.2.1, Objectives 1-5, p. 21).

2. All preterm infants $\leq$ 36 weeks, including infants < 1250g, with meningitis, were classified into those with "definite" and "possible" meningitis according to preset criteria – (see definitions below under Determination of Meningitis). The clinical course, responsible pathogens and laboratory findings between the two groups are described. All infants were followed to 18-months and outcomes are compared between infants with definite and possible meningitis. Prognostic variables that influenced outcome are elucidated. (See Section 1.3.2.2, Objectives 1-3, p. 22).

FIGURE 2.1. Schematic diagram of comparisons: (1) infants with definite meningitis vs. matched controls – lower portion of figure and (2) all infants with meningitis ≤36 weeks, definite vs. possible meningitis – middle portion of figure


Neonates with gestational age ≤ 36 weeks admitted to the Northern Alberta Neonatal Intensive Care Program, 01 January 1990 – 31 December 2003
Neonates with birth weight < 1250 g without meningitis
Neonates with gestational age ≤ 36 weeks diagnosed with meningitis in NICU – infants with "definite" and "possible" meningitis included in analysis
Control neonates with birth weight < 1250 g with no episode of meningitis, matched to neonates with meningitis (control:case = 2:1) by birth weight, gestational age, intracranial bleed, year of birth, singleton vs. multiple, and sex
Neonates with birth weight < 1250 g diagnosed with "definite" meningitis

2.1.2: Determination of meningitis

Infants constituting the groups were obtained from neonatal databases maintained at the Stollery Children's Hospital (SCH) and the Royal Alexandra Hospital (RAH) for all infants admitted to the Northern Alberta Neonatal Intensive Care Program. Neonatal database admission forms [Appendix 1 and 2] are completed in a paper format initially, detailing the infant's demographic data, reasons for admission, respiratory interventions, medications, diagnoses by organ system and discharge information. After the infant's discharge, the admission forms are completed and entered electronically into the database using the Paradox 7 program (1997).

From these databases all neonates with gestational age $\leq$ 36 weeks were identified. Any neonate with meningitis was determined by searching the databases for the terms "meningitis" or "cerebrospinal fluid (CSF) culture positive".

After patient chart review, infants with meningitis were further categorized as having definite meningitis, possible meningitis or meningitis because of growth of a contaminant from CSF according to the following criteria:

1. <u>Definite meningitis</u>
    a) pure growth of an organism from CSF culture with increased CSF white cell count (WCC) [>20 WCC if a non-bloody tap, or > 20 WCC and WCC: red blood cell (RBC) ratio of over 1:250] at initial or subsequent tap
    b) organism seen on gram stain of the CSF and later cultured even if WCC is normal

c) growth of Group B Streptococcus or *E. coli* from a non-bloody CSF even if the CSF WCC is normal

Note: If the organism cultured from CSF was a normal skin contaminant (e.g. coagulase-negative staphylococcus), the tap had to be non-bloody for a diagnosis of definite meningitis to be made if the blood cultures were positive for the same organism

2. Possible meningitis

a) negative CSF culture with increased CSF WCC (as defined above) and pretreatment with antibiotics

b) positive CSF culture for organism other than GBS or *E. coli* with a normal CSF WCC or CSF WCC not done

c) positive CSF and blood cultures for the same organism in the face of a bloody tap

d) any other case given over 72 hours antibiotics for "possible sepsis" that had either an increased CSF WCC or a positive CSF culture

3. Contaminant

a) Positive CSF culture with a common skin contaminant, normal CSF WCC, treated for < 72 hours with antibiotics with no recurrence.

b) Growth of organism from CSF in liquid media only

Infants with "meningitis" thought to be due to a contaminant were not reviewed further or included in the analyses.

This classification was used to ensure uniformity and degree of certainty of diagnosis of meningitis in preterm infants.

2.1.3: Controls

Two control infants were chosen for every infant with definite meningitis and BW < 1250g from infants who did not have meningitis. Matching was according to birth weight (± 100g), gestational age (± 1 week), and intracranial bleed (Papile grade 0, 1 or 2 vs. 3 or 4) (Papile, Burstein et al. 1978). In addition, controls were matched for year of birth (within 12 months), singleton vs. twin or triplet, and sex if possible. The matching criteria of gestational age, birth weight, intracranial bleed, singleton vs. multiple births, and sex, were chosen as all have been demonstrated to be risk factors for meningitis (Stoll, Gordon et al. 1996; Fanaroff, Korones et al. 1998; Stoll, Hansen et al. 2002) as well as predictors of outcome (Aziz, Vickar et al. 1995; Hack, Wilson-Costello et al. 2000; Vohr, Wright et al. 2000; Wood, Costeloe et al. 2005). Year of birth was matched so as to ensure that any changes in neonatal care would be consistent between cases and controls.

The number of controls, two controls for every case in this study, was chosen to increase the power of the study and to improve statistical efficiency (point estimates [ORs] and confidence intervals). In terms of feasibility, it was difficult to obtain more than two controls for each case using the matching criteria defined above.

The neonatal database at the Neonatal and Infant Follow-up Clinic was used to identify control infants. For each case, four matching criteria, birth weight, gestational age, intracranial bleed and year of birth, were initially used to identify control infants. Generally, this search yielded 2-4 control infants. Approximately 100 neonates with BW < 1250g are admitted to the Northern Alberta Neonatal Intensive Care Program per year. In order to match infants for all four criteria, in particular intracranial bleed, it was not

surprising that our yield was small per case. The most difficult matching criterion was degree of intracranial bleed. If more than two controls were identified, the other two matching criteria, sex and singleton vs. multiple birth, were applied. If the matching yielded less than two infants, we then searched for infants with a date of birth beyond 12 months of the case infant.

Patients in the Neonatal and Infant Follow-up database are identified by numerical code only. Only once the two controls had been chosen for each case were the names revealed to obtain the hospital records.

During the matching process, outcomes of the infants, cases and controls were not known. A potential flaw with not knowing the infants' outcomes, in particular death, was that the cases and controls would differ in terms of their chances of developing meningitis. For instance, if the control infant died early in their neonatal course, and thus could not develop meningitis, controls could appear worse in terms of their outcomes. In order to assess this aspect, the date of onset meningitis for the cases and the date of death/length of stay between cases and controls was observed and reported.

2.1.4: Inclusion criteria

1. Gestational age ≤36 weeks

All live born infants from northern and central Alberta with birth weight (BW) < 1250g are admitted to the Northern Alberta Neonatal Intensive Care Program to receive tertiary level care at either the SCH or RAH NICUs. During the 14-year study period, January 1990 to December 2003, 1603 live born infants with BW < 1250g were admitted to these tertiary care units. All infants with BW < 1250g are followed as a standard of

care by the Neonatal and Infant Follow-up Clinic at the Glenrose Rehabilitation Hospital where outcome parameters are available under numerical identification.

Infants born ≤ 36 weeks, but > 1250g are admitted to the SCH or RAH NICUs only if inborn or if intensive care services such as ventilation, are required. Infants from this category who are included in this study are thus a select group of infants with severe disease who require intensive care, rather than representative of all neonates born ≤ 36 weeks but > 1250g. During the study period, 9592 infants ≤ 36 weeks gestation were admitted to the NICUs. Infants ≤ 36 weeks but > 1250g are identified in the NICU for follow-up at the Glenrose Neonatal and Infant Follow-up Clinic on the basis of having had a major neurological complication such as meningitis in the neonatal period.

2. Definite or possible meningitis (bacterial or fungal)
3. Matched controls for infants with definite meningitis < 1250g.

2.1.5: Exclusion criteria

1. Chromosomal anomaly or clinically recognizable syndrome
2. Major congenital central nervous system malformation, e.g. neural tube defect
3. Confirmed congenital infection.

2.1.6: Definitions of adverse outcomes (death or disability)

The Neonatal and Infant Follow-up Clinic at the Glenrose Rehabilitation Hospital is a well-established centre for neonatal follow-up. For this study, the physical and sensory disabilities were documented at 18-24 months adjusted age (calculated according to post conceptual age rather than chronologic age from the time of birth). Assessment was done by a multidisciplinary team familiar with neonatal follow-up. The assessment at 18 months of adjusted age included: 1) medical and social history, interim

hospitalizations and therapeutic interventions; 2) physical and neurological examination, including growth parameters, completed by a nurse and pediatrician; 3) standardized motor examination by physiotherapist, occupational therapist, physiatrist as required; 4) neurosensory assessment including visual (ophthalmologic report) and auditory testing by certified audiologists; and 5) psychological assessment, the Bayley Scale of Infants Development by certified psychologist. The revised Bayley Scales of Infant Development II (BSID-II) (Bayley 1993) was used in Neonatal Follow-up clinic from 1993. Bayley scale scores provide a Mental Developmental Index (MDI) with a mean score of 100 and standard deviation (SD) of 15. Infants judged to be so severely delayed that they were untestable, were assigned a score of 49.

Adverse outcomes were defined as death (in the NICU or after discharge prior to 18-24 months age) or disability. Disability was defined as one or more of the following: (1) cognitive delay [>2SD below the mean of standardized testing - MDI < 70]; (2) cerebral palsy (CP) of all types and severity (Bax 1964; Levine 1980); (3) sensorineural hearing loss of > 40dB in the better ear; (4) visual impairment (vision < 20/60) or legal blindness (vision < 20/200) in the best eye following correction of refractive error, or (5) epilepsy. Infants with two or more of the above deficits were considered to be multiply disabled. This method of follow-up has been described previously (Robertson, Hrynchyshyn et al. 1992; Robertson, Sauve et al. 1994).

2.1.7: Ethics

Approval from the Research Ethics Board of the Faculty of Medicine and Dentistry of the University of Alberta was obtained in order to search databases and review the neonatal charts (Appendix 3).

Section 2.2: Data collection and preparation

Demographic, obstetric and neonatal data were extracted from database records from the NICUs at the RAH and SCH, and from neonatal hospital records. Outcomes at 18-24 months corrected age were obtained from the Neonatal and Infant Follow-up database. Data from every infant was recorded on a case report form [Appendix 4 and 5], designed specifically for this study, and then entered into an SPSS database.

2.2.1: Data from the neonatal period

2.2.1.1: For all infants

- Date of birth
- Birth weight (grams) and birth weight percentile by gestational age, sex and singleton vs. multiple birth for Albertan live born infants (Robertson, Svenson et al. 2002). Infants with a birth weight (BW) percentile < 10% were considered to have intrauterine growth restriction (IUGR)
- Gestational age (weeks)
- Sex
- Singleton vs. multiple gestation (twin or triplet)
- Maternal risk factors: prolonged rupture of membranes ≥ 18 hours, clinical chorioamnionitis, maternal fever ≥ 38°C, use of intrapartum antibiotics, maternal group B streptococcal status
- Antenatal steroid use
- Mode of delivery (vaginal vs. cesarean section)
- Inborn vs. outborn status
- Apgar scores

- Respiratory distress syndrome (RDS)
- Hypotension requiring inotrope/pressor support e.g. dopamine infusion
- Patent ductus arteriosus (PDA) requiring indomethacin only, or indomethacin and surgical ligation for closure
- Necrotizing enterocolitis (NEC) Bell stage II or III at any time during the NICU course (Bell, Ternberg et al. 1978)
- NEC requiring laparotomy for intestinal perforation or non-response to conservative management
- Chronic lung disease (CLD) defined as continued supplemental oxygen requirement at 36 weeks postconceptual age
- Postnatal corticosteroid treatment for respiratory failure
- Doxapram therapy for apnea of prematurity (Sreenan, Etches et al. 2001)
- Highest grade of retinopathy of prematurity (ROP) (ICROP, 2005)
- Retinal laser ablation for ROP (Andersen and Phelps 2000)
- Highest grade intraventricular hemorrhage (IVH) (Papile, Burstein et al. 1978). Severe IVH was defined as intraventricular hemorrhage with ventricular dilatation (grade 3 IVH) and/or intraparenchymal involvement (grade 4 IVH)
- Presence of periventricular leukomalacia (PVL) (Dubowitz, Bydder et al. 1985)
- Presence of a ventricular reservoir or ventriculoperitoneal (VP) shunt
- Hearing assessment, either otoacoustic emission testing or auditory brainstem responses, prior to discharge from the NICU – normal or abnormal.
- Duration of stay in the level III NICU (days)
- Death in hospital, age at death (days) and cause of death

Birth weight, gestational age and duration of stay in the level III NICU are continuous variables. Apgar scores and grade of ROP and IVH are ordinal variables. The rest of the variables are dichotomous variables (yes/no) and coded 0 (no exposure or outcome not present) and 1 (exposure or outcome present). Because the study design is a retrospective review, some information, particularly the obstetric data, was difficult to ascertain from chart review and was thus "unknown". A decision was made to code this information as "no" as it was presumed that if these details were clinically relevant, they would have been recorded in the chart. For infants who died early during their NICU course prior to the development of later sequelae of prematurity such as chronic lung disease (death prior to 36 weeks adjusted age) or retinopathy of prematurity (death prior to approximately 32 weeks or ophthalmologic examination), these outcomes were coded as "died in NICU" rather than "no".

2.2.1.2: For infants with meningitis

- Infants < 1250g with definite meningitis were coded as 1 and controls as 0.
- For all infants ≤36 weeks gestation, definite meningitis was coded as 1 and possible meningitis as 0
- Postnatal age at time of diagnosis of meningitis (days). "Early onset meningitis" (EOM) was defined as meningitis diagnosed ≤72 hours after birth. "Late onset meningitis" (LOM) was defined as meningitis diagnosed > 72 hours after birth (Stoll, Hansen et al. 2002; Stoll, Hansen et al. 2005)
- Clinical signs and symptoms of meningitis or sepsis occurring within 48 hours before and/or after the diagnostic spinal tap:

- Central nervous system(CNS) manifestations: lethargy, hypotonia, decreased level of consciousness
- Temperature instability: hypo-or hyperthermia - < 36° C or ≥38° C respectively
- Respiratory symptoms: respiratory distress, increased oxygen requirements > 10% above the child's usual baseline, increased or new onset apnea or bradycardias
- Gastrointestinal symptoms: increasing gastric aspirates or bilious aspirates, vomiting, abdominal distension, bloody stool
- Hypoglycemia < 2.5mmol/l or hyperglycemia > 10mmol/l

- Presence of seizures at the time of diagnosis (within 48 hours): clinical and/or electroencephalographic, or need for anti-epileptic drug therapy
- Concurrent conditions predisposing to or complications arising from meningitis:
  - Associated NEC (Bell's stage II or III) (Bell, Ternberg et al. 1978)
  - Associated hypotension requiring inotropic support
  - Presence of a central vascular line at the time of diagnosis of meningitis
  - Presence of a ventricular reservoir at the time of diagnosis of meningitis
  - Hyponatremia – sodium < 130mmol/l suggestive of SIADH
- Causative organism and antibiotic susceptibility patterns from CSF or blood cultures
- Cerebrospinal fluid parameters including WCC (x 10^6/L) and differential, RBC (x 10^6/L), gram stain, protein (g/L) and glucose concentration (mmol/L) at the time of diagnosis
- Peak CSF WCC (x 10^6/L)

- Peak CSF protein level (g/L)
- Peripheral complete blood count at initial diagnosis of meningitis including WCC (x 10^9/L) and platelet count (x 10^9/L)
- Serum blood glucose done at the time of LP (mmol/L)
- Positive cultures from blood concurrent with meningitis
- Radiographic findings or changes, specifically, serial head ultrasound scans after diagnosis of meningitis

Postnatal age at the time of diagnosis of meningitis, CSF WCC and RBC, CSF protein and glucose are continuous variables. Causative organism and antimicrobial susceptibility patterns, and radiographic findings are descriptive variables. All other variables were considered dichotomous (yes/no) and were coded 0 (no exposure or outcome not present) and 1 (exposure or outcome present). For the presenting signs and symptoms, presence of seizures at the time of diagnosis, and concurrent conditions predisposing to or complications arising from meningitis, any description of these parameters or evidence supporting the presence of these variables in the physician or nursing notes was coded as "yes", and if not mentioned, were coded as "no". If an infant had more than one episode of meningitis, details of the first episode only were analyzed.

2.2.2: Data from the Neonatal and Infant Follow-up

- Numbers of infants alive and available for follow-up at 18 months
- Death after discharge from the NICU, age and possible cause
- Number of infants lost to follow-up

- MDI from the Bayley scores. The MDI was also treated as a dichotomous variable with cutoffs i.e. < 70 for moderate cognitive delay, and < 55 for severe cognitive delay
- Disability defined as one or more of cerebral palsy, mental delay [MDI < 70], visual impairment , sensorineural hearing loss or epilepsy. Infants with two or more deficits were considered multiply disabled
- Shunt-dependent hydrocephalus
- Composite outcome of death (in the NICU or after discharge prior to the 18-month evaluation) or disability (as defined above)

MDI from the Bayley scores is a continuous variable. Other outcomes were entered as dichotomous variables (yes/no) and were coded 0 (outcome not present) and 1 (outcome present).

Section 2.3: Sample size and statistical analysis

2.3.1: Sample size

In order to achieve the primary objective of elucidating the outcomes of infants with BW < 1250g with definite meningitis (cases) in comparison to those who do not develop meningitis (controls), a sample of 12 infants with meningitis and 24 controls (2 controls: 1 case), would be able to detect an unadjusted mean difference in MDI score (continuous variable) of 15 with a SD of 15 using a two-sided test, with an alpha of 0.05 and beta of 0.80.

From January, 1990 to December, 2003, 68 neonates with GA $\leq$36 weeks were diagnosed with definite or possible meningitis. Of these, 49 infants had BW < 1250g. Nineteen infants with BW < 1250g had definite meningitis, 12 of whom survived to 18 months and were available for follow-up.

2.3.2: Data analysis

Univariate analysis of demographic, obstetric, neonatal and outcome data are expressed as frequencies and percentages or mean $\pm$ SD, using standard parametric or non-parametric statistics according to normality testing. Bivariate analysis between groups was assessed using Students t-test (continuous parametric) and Chi-square test or Fisher's exact test (dichotomous/categorical variables).

Conditional logistic regression was used to compare cases and matched controls to identify risk characteristics for meningitis (dependent variable – meningitis). Outcomes – composite outcome of death or disability, death in the NICU or before 18 months, and component disabilities were compared between infants with and without meningitis by unconditional logistic regression with matched clusters (case, control 1,

control 2). Prognostic variables influencing adverse outcome, death or disability, were ascertained by unconditional logistic regression with matched clusters. Predictive variables for MDI were determined by linear regression with matched clusters.

Unconditional logistic regression was used to compare the infants with definite and possible meningitis ≤36 weeks for baseline neonatal and maternal characteristics, clinical manifestations of meningitis, and neurodevelopmental outcomes. Unconditional logistic regression was also used to ascertain prognostic factors for outcome (dependent variable – death or disability as a composite outcome).

In order to determine the best subset of predictors and the best fitting regression model for the two comparison groups [(1) definite meningitis vs. controls < 1250g and (2) all infants ≤36 weeks, definite vs. possible meningitis], variables found to be significant at $p < 0.1$ or if too many variables were identified, $p < 0.05$, using univariate regression analysis were fitted into multivariate models to assess the effects of meningitis and other factors on the composite outcome of death or disability and the MDI score. Multivariate analysis was done using conditional and unconditional logistic regression for dichotomous outcome variables and linear regression for continuous variables.

For all variables of primary interest, odds ratios (OR) and 95% confidence intervals (CI) are reported.

Data were analyzed with the Statistical Program for Social Sciences (SPSS) version 12.0 for Windows (Microsoft). Stata (Stata Corp, College Station, Tex) was used specifically for conditional and unconditional logistic regression analyses with matched clusters. The level of significance was set at 5%.

Chapter 3

Results

Newborns with birth weight < 1250g

Section 3.1: Incidence and case fatality rate of meningitis in infants < 1250g

During the 14-year study period January 1990 to December 2003, there were 9592 infants ≤ 36 weeks gestational age admitted to the Northern Alberta Neonatal Intensive Care Program at either the SHC or RAH NICUs (FIGURE 3.1). Of these infants ≤36 weeks, 79 were determined to have 'meningitis' according to the neonatal databases.

During that time period, 1603 infants were admitted with birth weight < 1250g. Of these infants < 1250g, 57 were determined to have 'meningitis' according to the neonatal databases. When study criteria were applied, 19 had definite meningitis, 30 had possible meningitis and 8 had contaminated CSF (FIGURES 3.1, 3.2 and 3.3).

There were thus 49 infants diagnosed with meningitis (definite and possible) with BW < 1250g, giving an incidence of meningitis of 30 per 1000 in infants < 1250g. During the study period, there were 302 deaths in the NICU amongst the 1603 liveborn infants with BW < 1250g, an overall NICU mortality of 18%. There were 13 deaths in the NICU amongst the infants with BW < 1250g with meningitis. The case fatality rate due to meningitis was thus 27% amongst this very low birth weight group (FIGURE 3.2). Causes of death recorded from the charts included multi-organ failure (N = 2), severe intracranial bleed (N = 3), overwhelming sepsis (N = 3), respiratory failure (N = 4) and withdrawal of life-sustaining treatment (N = 1).

FIGURE 3.1. Flow diagram of the number of neonates with gestational age ≤ 36 weeks admitted to the Neonatal Intensive Care Unit (1990 - 2003), the infants in this group who developed meningitis, cases and controls < 1250g

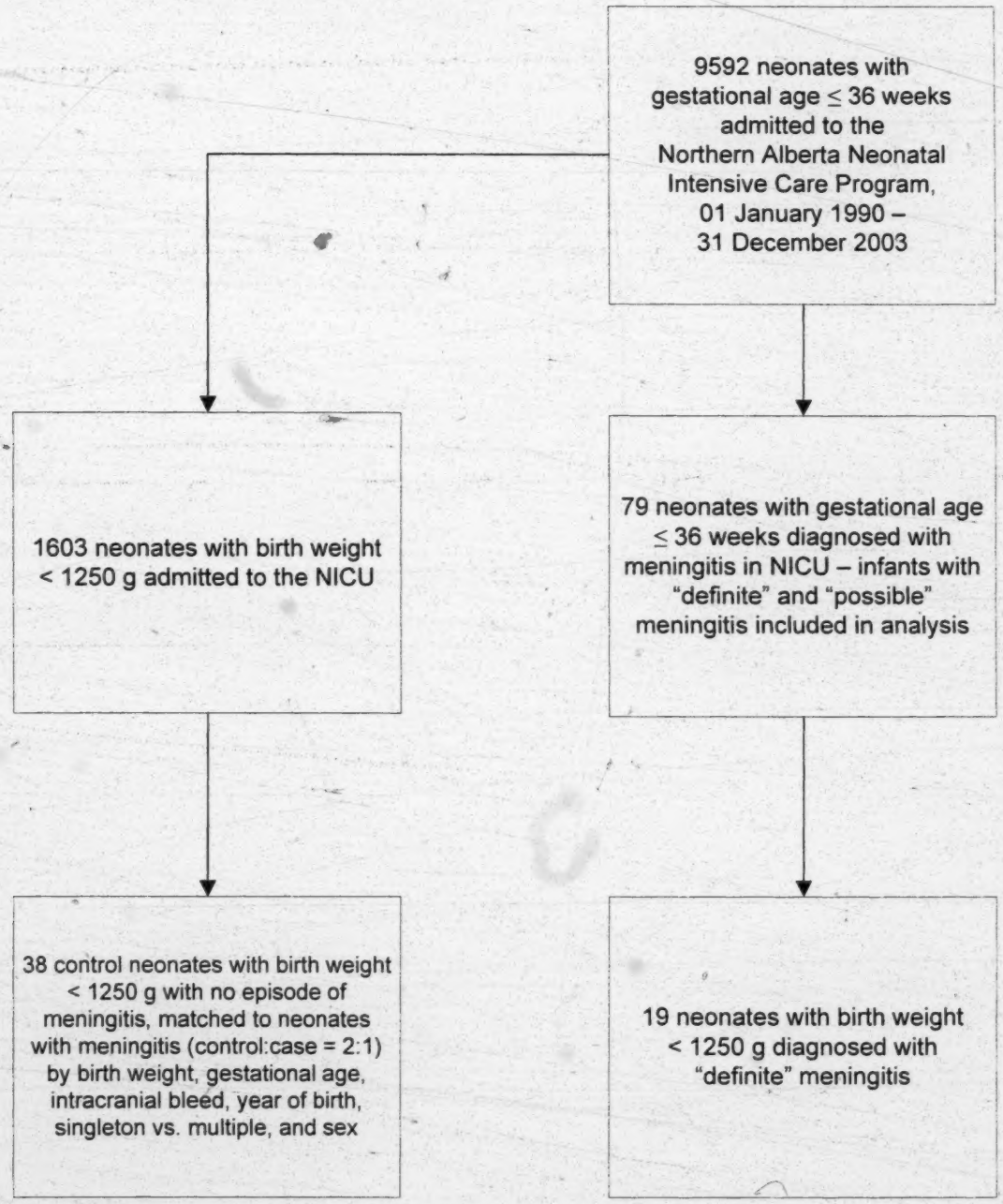

9592 neonates with gestational age ≤ 36 weeks admitted to the Northern Alberta Neonatal Intensive Care Program, 01 January 1990 – 31 December 2003
1603 neonates with birth weight < 1250 g admitted to the NICU
79 neonates with gestational age ≤ 36 weeks diagnosed with meningitis in NICU – infants with "definite" and "possible" meningitis included in analysis
38 control neonates with birth weight < 1250 g with no episode of meningitis, matched to neonates with meningitis (control:case = 2:1) by birth weight, gestational age, intracranial bleed, year of birth, singleton vs. multiple, and sex
19 neonates with birth weight < 1250 g diagnosed with "definite" meningitis

FIGURE 3.2. Flow diagram of the number of liveborn neonates with birth weight < 1250g admitted to the Neonatal Intensive Care Unit (1990 - 2003), the infants in this group who developed definite and possible meningitis, mortality and case fatality rate from meningitis

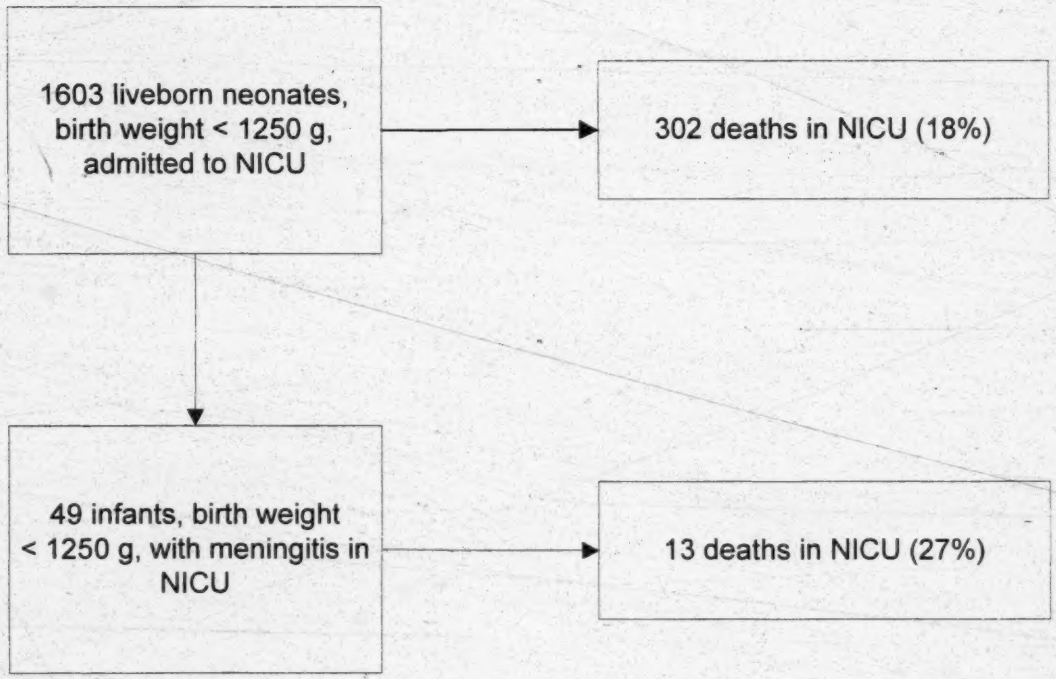
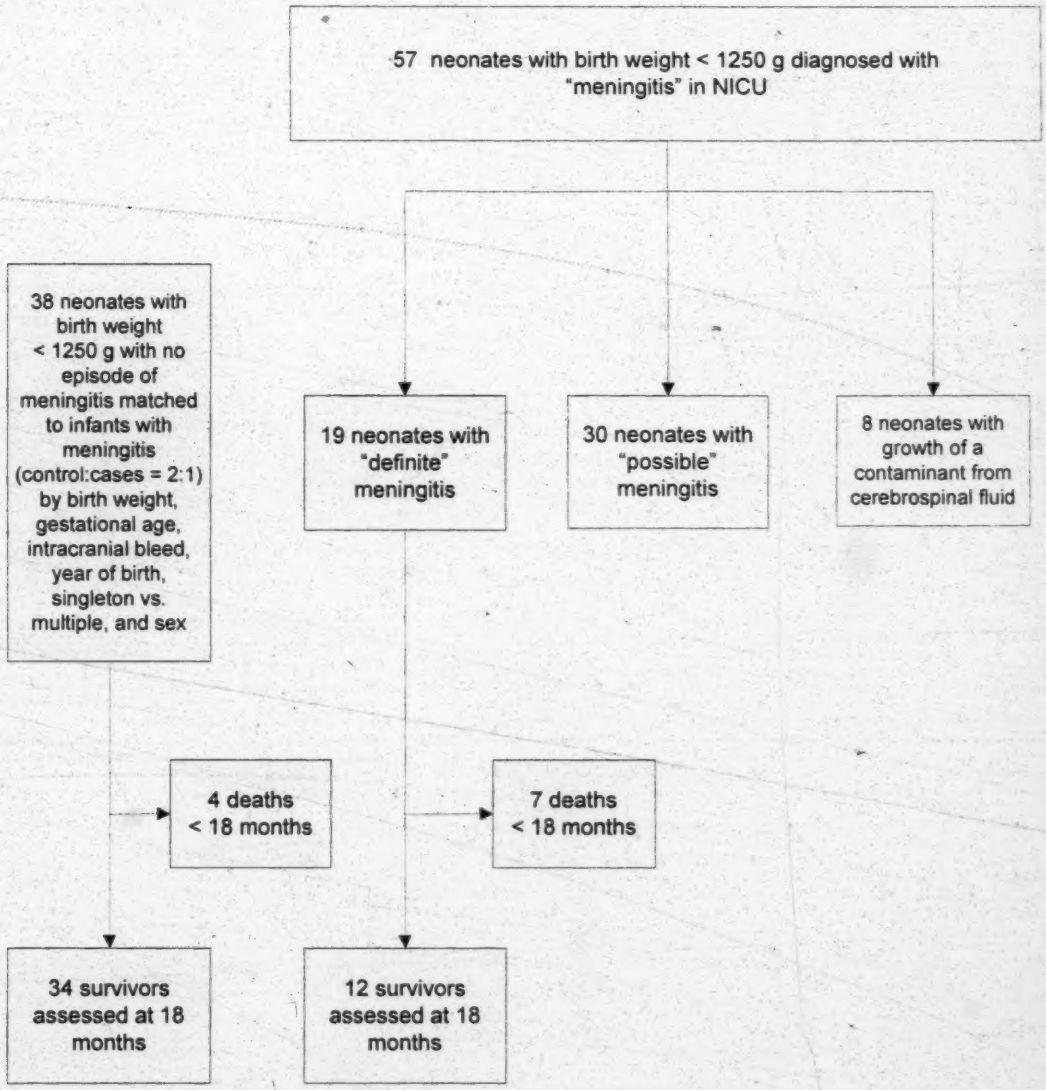

1603 liveborn neonates, birth weight < 1250 g, admitted to NICU
302 deaths in NICU (18%)
49 infants, birth weight < 1250 g, with meningitis in NICU
13 deaths in NICU (27%)

FIGURE 3.3. Flow diagram of infants < 1250 g diagnosed with 'meningitis' in the Northern Alberta Neonatal Intensive Care Program, 1990 – 2003. Nineteen infants with definite meningitis were identified and matched to 38 control infants. Survivors were followed to 18-months adjusted age


57 neonates with birth weight < 1250 g diagnosed with "meningitis" in NICU
38 neonates with birth weight < 1250 g with no episode of meningitis matched to infants with meningitis (control:cases = 2:1) by birth weight, gestational age, intracranial bleed, year of birth, singleton vs. multiple, and sex
19 neonates with "definite" meningitis
30 neonates with "possible" meningitis
8 neonates with growth of a contaminant from cerebrospinal fluid
4 deaths < 18 months
7 deaths < 18 months
34 survivors assessed at 18 months
12 survivors assessed at 18 months

Section 3.2: Selection of cases and controls for the nested case control study

The 19 infants with definite meningitis had 21 episodes of meningitis, i.e. two infants had two episodes of definite meningitis: [1] *C. albicans* followed by *E. coli* meningitis and [2] coagulase-negative staphylococcus followed by *Ureaplasma urealyticum* meningitis. Details of the first episode of meningitis only were considered in this study. Of the 19 infants, 18 had late-onset meningitis (diagnosed > 72 hours after birth). Organisms cultured from CSF included: *E. coli* (N = 4), CONS (N = 3), *C. albicans* (N = 3), Group B streptococcus (N = 2), *Enterococcus faecalis* (N = 2), *U. urealyticum* (N = 2), *Klebsiella pneumonia* (N = 1), *L. monocytogenes* (N = 1), and *S. aureus* (N = 1). The one infant with early-onset disease had meningitis with *L. monocytogenes*.

Using the matching criteria birth weight (± 100g), gestational age (± 1 week), intracranial bleed (Papile 0, 1 or 2 vs. 3 or 4), year of birth (within 12 months), singleton vs. twin or triplet, and sex, 2 controls were identified for every infant with definite meningitis (FIGURE 3.3). In order to ensure that cases and controls did not differ in terms of their chances of developing meningitis, the date of onset meningitis for the cases and the date of death/length of stay between cases and controls were observed. Of the 38 control infants, three infants in three different clusters died prior to the case infant developing meningitis.

Section 3.3: Clinical and risk characteristics for meningitis

Maternal and neonatal characteristics of the 19 infants with definite meningitis and 38 matched controls are presented in TABLE 3.1. There was no difference between the groups for the matching criteria: birth weight ($p = 0.90$), gestational age ($p = 0.92$), any IVH ($p = 1.00$), male sex ($p = 0.57$) and twin/triplet ($p = 1.00$).

Using conditional logistic regression (CLR) for matched data, antenatal corticosteroid exposure was a protective characteristic [52.6% vs. 78.9%; $p = 0.05$] and CLD a risk characteristic [81.3% vs. 60.0%; $p = 0.05$] associated with meningitis (TABLE 3.1). From the univariate analysis, five variables, maternal fever, antenatal corticosteroid exposure, cesarean section, CLD, and severe IVH had $p < 0.10$, so were entered into a multivariate model. This multivariate model was associated with an increased risk of meningitis ($p < 0.01$), but none of the individual variables were significant (TABLE 3.2).

Length of tertiary NICU stay (LOS) was not different between the two groups (TABLE 3.1 and FIGURE 3.4). Neonates who died in the NICU are plotted separately (6 neonates in the meningitis group and 3 in the control group). There is one outlier in the definite meningitis group whose LOS was 292 days.

More infants in the definite meningitis group required a ventricular reservoir in the NICU (TABLE 3.1) - of the 19 infants with definite meningitis, 8 (42.1%) required a ventricular reservoir in the NICU: 3 for posthemorrhagic hydrocephalus (PHH) after severe IVH and 5 for progressive hydrocephalus post-meningitis. In the control group, 1 (2.6%) infant required a reservoir for PHH after severe IVH.

TABLE 3.1. Comparison of maternal and neonatal characteristics of infants with definite meningitis (N = 19) and matched controls (N = 38) using univariate conditional logistic regression *

Characteristic	Definite meningitis	Matched controls	OR (95% CI)	p
Neonates				
Birth weight (grams) †	825 ± 181	818 ± 179	NA	0.90 ‡
Gestational age (weeks) †	25.8 ± 1.8	25.8 ± 1.9	NA	0.92 ‡
Male sex †	9 (47.4)	15 (39.5)	1.4 (0.5 – 4.2)	0.57 §
Twin or triplet †	3 (15.8)	7 (18.4)	0.8 0.2 – 3.7	1.00 ‖
Intrauterine growth restriction (BW < 10%)	2 (10.5)	6 (15.8)	0.4 (0 – 4.6)	0.49 ¶
Outborn	3 (15.8)	2 (5.3)	4.6 (0.5 – 46.9)	0.19 ¶
Apgar score at 5 minutes	7 ± 1	6 ± 2	1.4 (0.9 – 2.3)	0.18 ¶
Mothers				
Prolonged rupture of membranes	5 (26.3)	16 (42.1)	0.5 (0.2 – 1.7)	0.28 ¶
Chorioamnionitis	5 (26.3)	9 (23.7)	1.2 (0.3 – 5.2)	0.80 ¶
Maternal fever	5 (26.3)	3 (7.9)	4.3 (0.8 – 22.8)	0.08 ¶ **
GBS positive ††	2/3 (66.7)	1/6 (16.7)	NA	
Intrapartum antibiotics	11 (57.9)	29 (76.3)	0.5 (0.1 – 1.4)	0.18 ¶
Antenatal steroids	10 (52.6)	30 (78.9)	0.3 (0.1 – 1)	0.05 ¶ ** ‡‡
Cesarean section	6 (31.6)	21 (55.3)	0.3 (0.1 – 1.2)	0.08 ¶ **

Table 1 continued on pages 47 & 48

TABLE 3.1. (cont'd) Comparison of maternal and neonatal characteristics of infants with definite meningitis (N = 19) and matched controls (N = 38) using univariate conditional logistic regression *

Characteristic	Definite meningitis	Matched controls	OR (95% CI)	p
Neonatal course				
Respiratory distress syndrome	19 (100.0)	35 (92.1)	NA §§	
Hypotension requiring inotropes/pressors	13 (68.4)	23 (60.5)	1.8 (0.4 – 8.0)	0.46 ¶
Patent ductus arteriosus	14 (73.7)	29 (76.3)	0.8 (0.1 – 4.5)	0.77 ¶
Necrotizing enterocolitis Bell stage II/III	4 (21.1)	5 (13.2)	1.9 (0.4 – 8.9)	0.43 ¶
Laparotomy (NEC/intestinal perforation)	2 (10.5)	5 (13.2)	0. 7 (0.1 – 6.4)	0.73 ¶
Chronic lung disease ‖‖	13/16 (81.3)	21/35 (60.0)	9.1 (1.1 – 78.4)	0.05 ¶ ** ‡‡
Postnatal steroids	8 (42.1)	16 (42.1)	1 (0.3 – 3.7)	1.00 ¶
Doxapram for apnea of prematurity	12 (63.2)	23 (60.5)	1.2 (0.3 – 4.4)	0.82 ¶
Severe ROP (stage 3 or more) ‖‖	8/16 (50.0)	9/35 (25.7)	NA §§	
Retinal laser therapy for ROP ‖‖	3 (18.8)	6 (17.1)	1.3 (0.2 – 6.9)	0.77 ¶
Any intraventricular hemorrhage †	12 (63.2)	24 (63.2)	1 (0.3 – 3.1)	1.00 §
Severe IVH (grade III or IV)	10 (52.6)	14 (36.8)	6.6 (0.7 – 60.9)	0.10 ¶ **
Periventricular leukomalacia	7 (36.8)	9 (23.7)	3 (0.5 – 16.9)	0.22 ¶
Length of stay at tertiary site	98 ± 66	92 ± 44	1 (1 – 1.0)	0.63 ¶
Ventricular reservoir in NICU	8 (42.1)	1 (2.6)	NA §§	

* Plus – minus values are means ± SD; frequencies are no. (%)
† Analysis by conditional logistic regression was not done for the matching criteria used for selecting controls (birth weight, gestational age, singleton vs. twin/triplet, sex and intraventricular hemorrhage)
‡ Comparison by Student's t-test
§ Comparison by Chi square

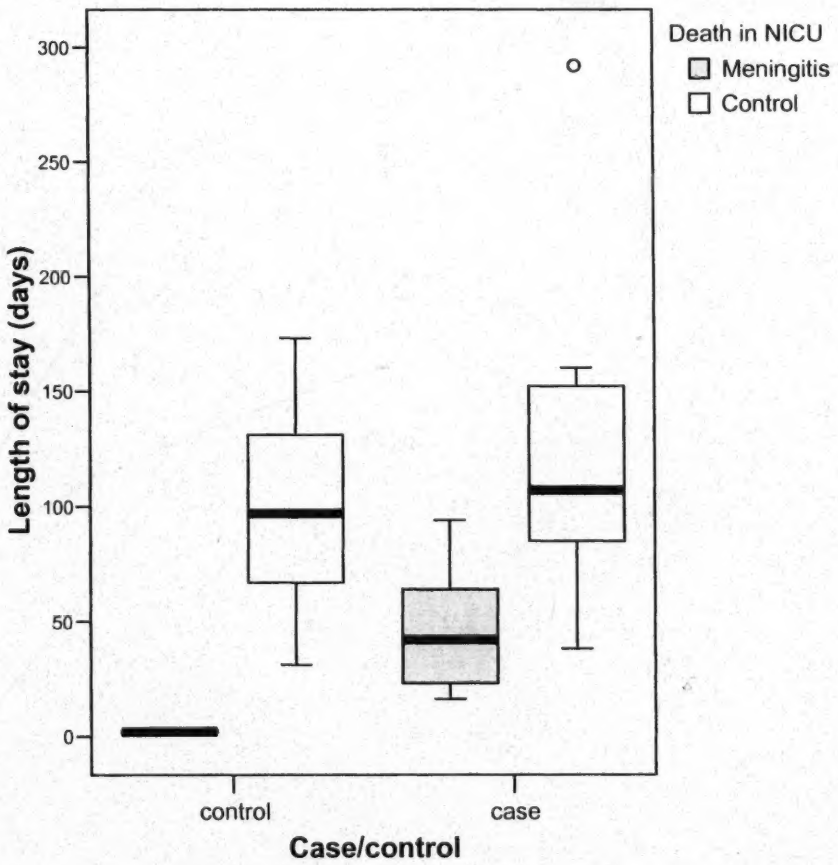
‖ Comparison by Fisher's Exact test
¶ Comparison by univariate conditional logistic regression for matched data
** $p < 0.10$ – risk characteristics entered into the multivariate model
†† A total of 9 mothers were swabbed for Group B Streptococcal status
‡‡ Significant difference between groups ($p < 0.05$)
§§ Unable to calculate
‖‖ Three infants in the definite meningitis group and three infants in the control group died prior to 32 weeks gestational age, and thus could not by definition develop chronic lung disease or retinopathy of prematurity

TABLE 3.2. Multivariate analysis using conditional logistic regression for risk characteristics for meningitis comparing infants with definite meningitis (N = 19) and matched controls (N = 38)

Characteristic	**OR (95% CI)**	**p ***
Overall model		< 0.01 †
Maternal fever	12.9 (0.8 – 197)	0.07
Antenatal steroid exposure	0.3 (0.1 – 1.9)	0.22
Cesarean section	0.4 (0 – 3.9)	0.43
Chronic lung disease	48.8 (0.9 – 2713)	0.06
Severe IVH	8.4 (0.4 – 183)	0.17

* Comparison by conditional logistic regression for matched data – variables with $p < 0.10$ from the univariate analysis were included
† Significant difference between groups ($p < 0.05$)

FIGURE 3.4. Boxplot graphs depicting length of tertiary NICU stay of neonates with definite meningitis (N = 19) and matched controls (N = 38), separating infants who died in the NICU



Section 3.4: Outcomes and prognostic variables of cases and controls

Outcomes were available at 18-months adjusted age for all infants, and are presented in TABLE 3.3. The composite outcome of death or disability was higher amongst infants with definite meningitis [84.2% vs. 50.0%; p = <0.01]. The incidence of mortality at 18 months (either in the NICU or after discharge) [36.8% vs. 10.5%; p = 0.03], any disability [75.0% vs. 44.1%; p = 0.04], cerebral palsy [41.7% vs. 8.8%; p = <0.01] and presence of a VP shunt [33.3% vs. 5.9%; p = 0.03] were higher in infants with definite meningitis.

Amongst infants with definite meningitis, causes of death in the NICU included multi-organ failure (N = 1), intracranial bleed (N = 1), respiratory failure (N = 1) and overwhelming sepsis (N = 3). Control infants died in the NICU from intracranial bleed (N = 1) and respiratory failure (N = 2). Both infants (one with definite meningitis and one control) who died after discharge from the NICU had respiratory failure.

Of the 8 infants with meningitis who required a ventricular reservoir for hydrocephalus in the NICU, 2 infants died in the NICU and 4 infants required insertion of a VP shunt. Further, all of these 8 infants had an adverse outcome, either death or one or more disabilities (TABLE 3.4). In the control group, 2 infants required placement of a VP shunt, one of whom had a ventricular reservoir in NICU for posthemorrhagic hydrocephalus. Both of these infants had cognitive delay, one with isolated cognitive delay and the other with multiple disabilities (spastic diplegia, hearing loss and cognitive delay).

There was no difference in the MDI scores of survivors between infants with definite meningitis and matched controls (TABLE 3.3, and FIGURES 3.5 and 3.6).

Infants who had a VP shunt in place at 18 months (6 infants in total – 4 who had definite meningitis in the NICU and 2 matched controls) had lower MDIs compared to infants who did not have a VP shunt (infants with VP shunt 56 $\pm$ 15; infants without VP shunt 72 $\pm$ 18; $p = 0.04$) (FIGURE 3.6).

Meningitis, hypotension, severe ROP, severe IVH and PVL were significant prognostic variables for adverse outcome (composite death or disability) in the univariate unconditional logistic regression with matched clusters (TABLE 3.5). The multivariate model predicted death or disability ($p < 0.01$) with meningitis (OR 5.4, $p = 0.02$) and severe IVH (OR 7.5, $p < 0.01$) the most significant variables (TABLE 3.6). All 10 infants (100%) with severe IVH with definite meningitis had an adverse outcome, and 11 of the 14 matched controls (78.6%) with severe IVH had an adverse outcome.

Several variables in the univariate linear regression showed an association with the infants' MDI as a continuous dependent variable: outborn status, severe IVH, severe ROP, length of tertiary NICU stay (LOS), and VP shunt at 18 months (TABLE 3.7). There were significant associations between severe ROP and severe IVH (OR 9.0, 95% CI 2.3 - 35; $p < 0.01$), severe IVH and VP shunt at 18 months (OR 1.4, 95% CI 1 - 1.9; $p < 0.01$), LOS and severe ROP (OR 1.0, 95% CI 1.0 – 1.0; $p < 0.01$), and LOS and severe IVH (OR 1.0, 95% CI 1.0 – 1.0; $p < 0.01$). There was no association between severe ROP and VP shunt (OR 1.1, 95% CI 0.2 - 6.6; $p = 0.94$), between VP shunt and LOS (OR 1.0, 95% CI 1.0 – 1.0; $p = 0.29$), outborn status and severe IVH (OR 0.9, 95% CI 0.1 – 5.9; $p = 0.9$), outborn status and severe ROP (OR 0.5, 95% CI 0 – 4.6; $p = 0.5$), outborn status and VP shunt at 18 months (OR 0.9, 95% CI 0.8 – 1.0; $p = 1$), and outborn status and LOS (OR 1.0, 95% CI 1.0 - 1.0; $p = 0.33$), thus these four variables (outborn status,

severe ROP, VP shunt at 18 months and LOS) were fitted in the multivariate model (TABLE 3.8). Presence of a VP shunt at 18 months predicted a lower MDI at 18 months (B coefficient –12.73, SE 6.22; p=0.05) in the multivariate model.

TABLE 3.3. Neurodevelopmental outcomes at 18-months adjusted age for infants with definite meningitis (N = 19) vs. matched controls (N = 38) – comparison by univariate unconditional logistic regression with matched clusters (1 infant with definite meningitis: 2 matched controls)

	Definite meningitis	**Matched controls**	**OR (95% CI)**	**p**
Outcome	No/total no. (%)			
Composite outcome				
Death or disability	16/19 (84.2)	19/38 (50.0)	5.3 (1.7 – 16.6)	<0.01*†
Components				
Death in NICU	6/19 (31.6)	3/38 (7.9)	5.4 (1.2 – 24.5)	0.03 *†
Death before 18 months	7/19 (36.8)	4/38 (10.5)	4.9 (1.1 – 21.5)	0.03 *†
Any disability	9/12 (75.0)	15/34 (44.1)	3.8 (1.1 – 13.6)	0.04 *†
Cerebral palsy	5/12 (41.7)	3/34 (8.8)	7.4 (2.0 – 26.6)	<0.01*†
Cognitive delay (MDI<70)	7/12 (58.3)	13/34 (38.2)	2.3 (0.6 – 8.1)	0.21 *
Hearing loss	2/12 (16.7)	2/34 (5.9)	3.2 (0.7 – 14.9)	0.14 *
Visual loss	2/12 (16.7)	2/34 (5.9)	3.2 (0.3 – 29.6)	0.34 *
Epilepsy	0	0		
Other outcomes at 18 months				
Ventriculoperitoneal shunt at 18 months	4/12 (33.3)	2/34 (5.9)	8.2 (1.2 – 55.4)	0.03 *†
Multiply disabled ‡	3/12 (25.0)	4/34 (11.8)	2.5 (0.8 – 8.2)	0.13 *
MDI (mean ± SD)	68.83 ± 22.51	70.85 ±17.11		0.75 §

* Comparison by univariate unconditional logistic regression with matched clusters
† Significant difference between groups ($p < 0.05$)
‡ Child affected by two or more disabilities
§ Comparison by Students t-test

TABLE 3.4. Neurodevelopmental outcomes at 18-months adjusted age for infants with definite meningitis requiring a ventricular reservoir in the Neonatal Intensive Care Unit with subsequent shunt dependent hydrocephalus

	Meningitis and pathogen	**Ventriculoperitoneal shunt**	**Neurodevelopmental outcome**
1	*Listeria monocytogenes*	Yes	Hemiplegia
2	*Candida albicans*	No	Spastic diplegia Cognitive delay Hearing loss
3	*Enterococcus faecalis*	Yes	Spastic quadriplegia Cognitive delay Hearing loss Vision loss
4	Coagulase negative staphylococcus	Death *	Death
5	*Ureaplasma urealyticum*	Yes	Cognitive delay
6	Coagulase negative staphylococcus	Yes	Hemiplegia Cognitive delay Vision loss
7	*Escherichia coli*	No	Cognitive delay
8	Coagulase negative staphylococcus	Death *	Death

* These infants died before 18 months and did not have a ventriculoperitoneal shunt placed prior to death

FIGURE 3.5. Bayley Mental Developmental Index (MDI) scores categorized by standard deviation for infants with definite meningitis (N = 19) and matched controls (N = 38). Bayley scale scores provide an MDI with a mean of 100 and SD of 15. Scores less than 70 are > 2SD and scores less than 55 are > 3SD below the mean of standardized testing

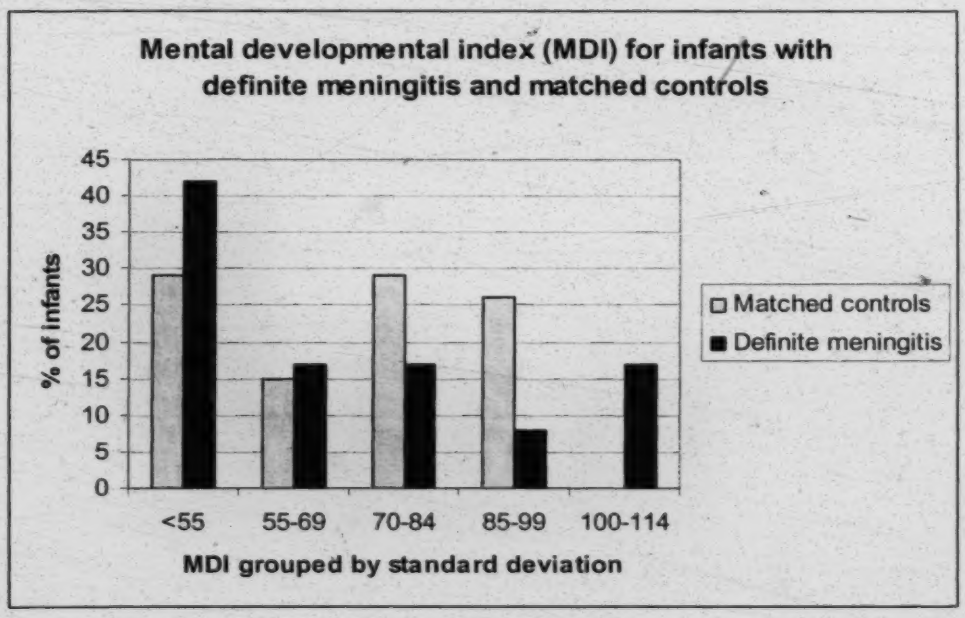


FIGURE 3.6. Boxplot graphs depicting Bayley Mental Developmental Index (MDI) scores of 19 neonates with definite meningitis and 38 matched controls, selecting for infants who had a ventriculoperitoneal shunt in place at 18 months.

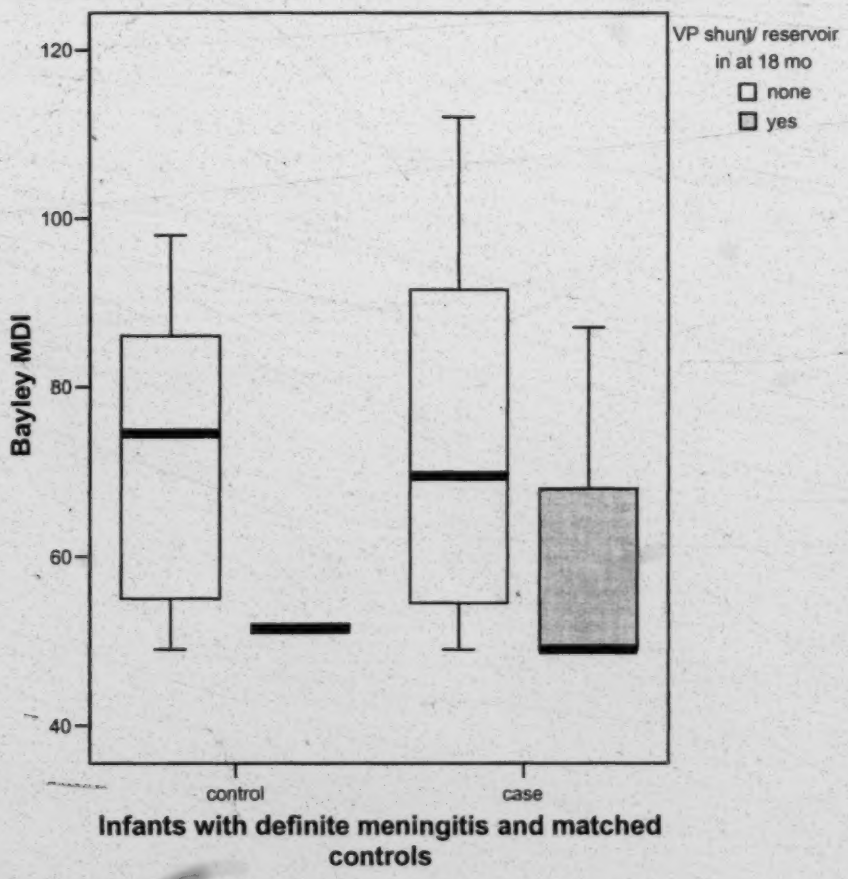


TABLE 3.5. Prognostic variables for adverse outcome (composite death or disability) using univariate unconditional logistic regression with matched clusters for 19 infants with definite meningitis and 38 matched controls*

Prognostic variable	OR	95% CI	p*
Definite meningitis	5.3	1.7 – 16.6	<0.01 †
Male sex	2.0	0.6 – 7.3	0.28
Twin or triplet	0.9	0.4 – 2.2	0.87
Intrauterine growth restriction	0.6	0.2- 2.2	0.43
Outborn	0.1	0 – 1.2	0.08
Apgar score 5 minutes	0.8	0.6 – 1.1	0.22
Prolonged rupture of membranes	0.5	0.2 - 1.6	0.28
Chorioamnionitis	0.8	0.3 - 2.1	0.64
Maternal fever	2.1	0.4 – 9.4	0.35
Intrapartum antibiotics	0.6	0.2 – 1.5	0.29
Antenatal steroids	1.5	0.4 – 5.8	0.59
Cesarean section	1.1	0.4 – 3.4	0.82
Respiratory distress syndrome	3.4	0. 8 - 14.9	0.10
Hypotension	4.9	1.5 – 15.9	0.01 ‡
Patent ductus arteriosus	1.3	0.4 – 4.3	0.71
NEC Bell stage II/III	2.5	0.5 – 13.1	0.29
Laparotomy	1.7	0.4 – 6.5	0.46
Chronic lung disease	3.8	0.9 – 15.9	0.06
Postnatal steroids	2.8	0.9 – 8.6	0.07
Doxapram for apnea of prematurity	0.4	0.2 - 1.2	0.11
Severe ROP (stage 3 or more)	5.9	1.5 – 23.3	0.01 †
Retinal laser therapy for ROP	1.6	0.5 – 5.5	0.41
Severe IVH (grade III or IV)	9.5	2.6 – 34.1	<0.01 †
Periventricular leukomalacia	3.2	1.1 – 9.1	0.03 †
Length of tertiary NICU stay	1.0	1.0 - 1.0	0.26
VP shunt at 18 months ‡	NA		

* Comparison by unconditional logistic regression with matched clusters (1 infant with definite meningitis: 2 matched controls)

† Significant difference between groups ($p < 0.05$) – variables entered into multivariate model

‡ Unable to calculate as all infants with VP shunt at 18 months had a disability

TABLE 3.6. Multivariate analysis using unconditional logistic regression with matched clusters for prognostic variables for adverse outcome (composite death or disability), comparing infants with definite meningitis (N = 19) and matched controls (N = 38) *

Characteristic	**OR (95% CI)**	**p ***
Overall model		< 0.01 †
Meningitis	5.4 (1.3 – 22.7)	0.02 †
Hypotension	1.2 (0.2 – 6.7)	0.81
Severe ROP (stage 3 or more)	2.4 (0.6 – 9.8)	0.22
Severe IVH (grade III or IV)	7.5 (1.8 – 31.3)	< 0.01 †
Periventricular leukomalacia	1.9 (0.7 – 5.3)	0.24

* Comparison by unconditional logistic regression with matched clusters (1 infant with definite meningitis: 2 matched controls) – variables with $p < 0.05$ were included

† Significant difference between groups ($p < 0.05$)

TABLE 3.7. Predictive variables for Mental Developmental Index (MDI), a continuous dependent variable, using simple linear regression with matched clusters for 19 infants with definite meningitis and 38 matched controls *

Predictive variable	B coefficient	SE	p †
Definite meningitis	- 2.02	7.00	0.78
Intrauterine growth restriction	3.09	6.74	0.65
Outborn	15.57	5.43	0.01 ‡
Apgar score 5 minutes	1.69	1.37	0.23
Prolonged rupture of membranes	0.42	5.99	0.95
Chorioamnionitis	- 3.42	5.96	0.57
Maternal fever	0.76	9.47	0.94
Intrapartum antibiotics	5.44	5.12	0.30
Antenatal steroids	- 4.02	6.53	0.55
Cesarean section	- 4.28	6.64	0.53
Respiratory distress syndrome	2. 84	6.42	0.66
Hypotension	- 4.74	5.69	0.42
Patent ductus arteriosus	- 5.66	5.97	0.36
NEC Bell stage II/III	1.13	8.17	0.89
Laparotomy (NEC/intestinal perforation)	- 6.89	8. 05	0.40
Chronic lung disease	- 6.48	4.93	0.21
Postnatal steroids	- 8.80	5.07	0.10
Doxapram for apnea of prematurity	3.09	5.67	0.59
Severe ROP (stage 3 or more)	- 12.38	5.04	0.02 ‡
Retinal laser therapy for ROP	- 8.57	6.22	0.19
Severe IVH (grade III or IV)	- 14.99	4.34	<0.01 ‡
Periventricular leukomalacia	- 2.76	5.61	0.63
Length of tertiary NICU stay	- 0.15	0.05	<0.01 ‡
VP shunt at 18 months	- 16.28	6.66	0.03 ‡

* Birth weight, gestational age, male gender, twin/triplet and intraventricular hemorrhage were not included in this analysis as these are matching criteria for the control group

† Comparison by linear regression with matched clusters (1 infant with definite meningitis: 2 matched controls)

‡ Significant association ($p < 0.05$)

TABLE 3.8. Multivariate analysis for multiple linear regression for prognostic variables for Mental Developmental Index at 18 months with matched clusters for the 19 infants with definite meningitis and 38 matched controls *

Predictive variable	B coefficient	SE	p *
Overall model			<0.01 †
Outborn	9.85	7.60	0.21
Severe ROP (stage 3 or more)	- 7.76	5.18	0.15
Length of tertiary NICU stay	- 0.08	0.06	0.16
VP shunt at 18 months	- 12.73	6.22	0.05 †

* Comparison by linear regression with matched clusters (1 infant with definite meningitis: 2 matched controls) – variables from the univariate analysis with $p < 0.05$ were included

† Significant association ($p < 0.05$)

Chapter 4

Results

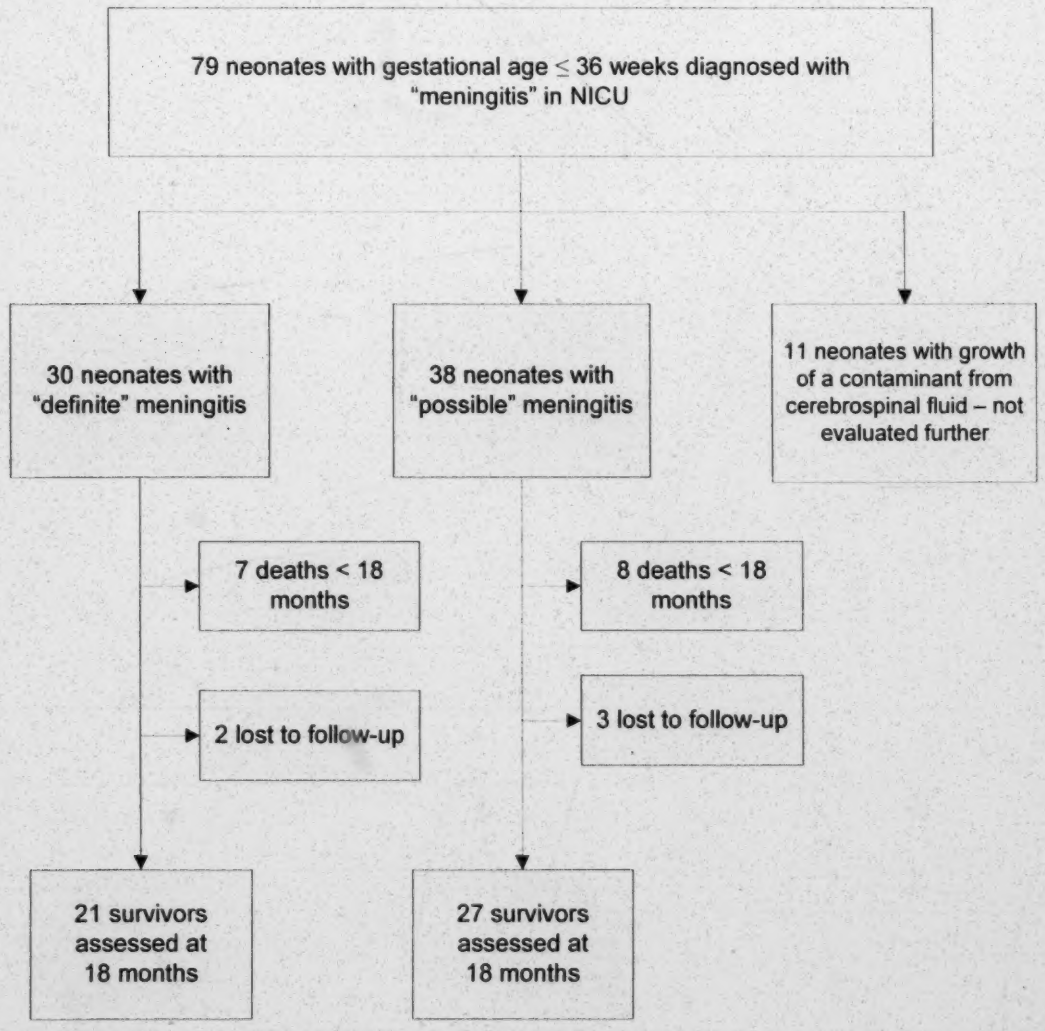
Meningitis in premature neonates ≤36 weeks gestation – comparison of infants with definite and possible meningitis

Section 4.1: Study population

During the 14-year study period, January 1990 to December 2003, there were 79 newborns with gestational age ≤36 at birth who had a diagnosis of 'meningitis' during their hospital stay at either the SCH or RAH NICUs (FIGURE 3.1). When study criteria were applied, 30 had definite meningitis, 38 had possible meningitis, and 11 had contaminated CSF (FIGURE 4.1).

Among the 68 newborns with definite and possible meningitis, there were 72 episodes of meningitis: two newborns had two episodes of definite meningitis - (1) *C. albicans* followed by *E. coli* meningitis and (2) CONS followed by *U. urealyticum* meningitis, one newborn had one episode of definite meningitis (*U. urealyticum*) followed by an episode of possible meningitis (no organism identified in CSF or blood culture), and one newborn had two episodes of possible meningitis (both CONS). Details of the first episode of meningitis only are included in this analysis.

FIGURE 4.1. Flow diagram of infants ≤36 weeks gestational age diagnosed with 'meningitis' in the Northern Alberta Neonatal Intensive Care Program, 1990 – 2003. Infants with definite and possible meningitis were identified and followed to 18-months adjusted age


79 neonates with gestational age ≤ 36 weeks diagnosed with "meningitis" in NICU
30 neonates with "definite" meningitis
38 neonates with "possible" meningitis
11 neonates with growth of a contaminant from cerebrospinal fluid – not evaluated further
7 deaths < 18 months
8 deaths < 18 months
2 lost to follow-up
3 lost to follow-up
21 survivors assessed at 18 months
27 survivors assessed at 18 months

Section 4.2: Baseline neonatal and maternal characteristics, and clinical manifestations of meningitis

Baseline neonatal and maternal characteristics of the 30 newborns with definite meningitis and 38 newborns with possible meningitis are presented in TABLE 4.1. The groups were similar in gestational age, birth weight, and maternal and neonatal complications except that neonates with possible meningitis were more likely to have been hypotensive requiring inotropic/pressor support during their NICU course [53.3% vs. 78.9%; p = 0.03]. Mortality in the NICU was similar between the two groups [20.0% vs. 18.4%; p = 0.87] (TABLE 4.1).

Most newborns in both groups had late-onset meningitis [90.0% vs. 92.1%; p = 0.76] (TABLE 4.2). The manifestations of meningitis were non-specific. Newborns with definite meningitis were more likely to have had seizures at the time of diagnosis [56.7% vs. 31.6; p = 0.04]. Newborns with possible meningitis were more likely to have a central intravascular catheter in place at the time of diagnosis [53.3% vs. 78.9; p = 0.03].

Of the ten infants who had a ventricular reservoir in place at the time of meningitis, seven appeared to have meningitis related to the presence of the reservoir with positive CSF cultures obtained from tapping the reservoir. These infants had infection with *C. albicans* (N = 2), CONS (N = 3), *E. faecalis* (N = 1) and Clostridium not perfringens (N = 1).

TABLE 4.1. Baseline neonatal and maternal characteristics of infants with meningitis * †

Characteristic	Definite meningitis (N = 30)	Possible meningitis (N = 38)	OR (95% CI)	p
Neonates				
Birth weight (grams)	1139 ± 502	953 ± 448	1 (1 – 1)	0.12
Gestational age (weeks)	27.5 ± 3.0	26.5 ± 2.6	1.1 (1 – 1.3)	0.14
Birth weight < 1250g	19 (63.3)	30 (78.9)	0.5 (0.1 – 1.3)	0.16
Gestational age < 28 weeks	16 (53.3)	27 (71.1)	0.5 (0.2 – 1.3)	0.13
Male sex	17 (56.7)	21 (55.3)	1 (0.4 – 2.8)	0.91
Twin or triplet	3 (10.0)	8 (21.1)	0.4 (0.1 – 1.7)	0.23
Intrauterine growth restriction (BW < 10%)	2 (6.7)	6 (15.8)	0.4 (0.1 – 2.0)	0.26
Outborn	9 (30.0)	6 (15.8)	2.3 (0.7 – 7.4)	0.17
Apgar score at 5 minutes	7 ± 1	6 ± 2	1.4 (1 – 1.9)	0.06
Mothers				
Prolonged rupture of membranes	10 (33.3)	11 (28.9)	1.2 (0.4 – 3.4)	0.4
Chorioamnionitis	8 (26.7)	4 (10.5)	3.1 (0.8 – 11.5)	0.09
Maternal fever	6 (20.0)	6 (15.8)	1.3 (0.4 – 4.7)	0.65
GBS positive ‡	3/6 (50.0)	4/11 (36.4)	1.8 (0.2 – 13.1)	0.59
Intrapartum antibiotics	19 (63.3)	17 (44.7)	2.1 (0.8 – 5.7)	0.13
Antenatal steroids	16 (53.3)	17 (44.7)	1.4 (0.5 – 3.7)	0.48
Cesarean section	9 (30.0)	6 (15.8)	0.8 (0.3 – 2.3)	0.66

Table 1 continued on pages 65 & 66

TABLE 4.1. (cont'd) Baseline neonatal and maternal characteristics of infants with meningitis * †

Characteristic	Definite meningitis (N = 30)	Possible meningitis (N = 38)	OR (95% CI)	p
Neonatal course				
Respiratory distress syndrome	24 (80.0)	33 (86.8)	0.6 (0.2 – 2.2)	0.45
Hypotension requiring inotropes/pressors	16 (53.3)	30 (78.9)	0.3 (0.1 – 0.9)	0.03 §
Patent ductus arteriosus	18 (60.0)	27 (71.1)	0.6 (0.2 – 1.7)	0.34
Necrotizing enterocolitis Bell stage II/III	6 (20.0)	11 (28.9)	0.6 (0.2 – 1.9)	0.40
Laparotomy (NEC/intestinal perforation)	2 (6.7)	11 (28.9)	0.2 (0 – 1.2)	0.08
Chronic lung disease ‖	13/26 (50.0)	24/33 (72.7)	0.4 (0.1 – 1.1)	0.08
Postnatal steroids	10 (33.3)	15 (39.5)	0.8 (0.3 – 2.1)	0.60
Doxapram for apnea of prematurity	14 (46.7)	19 (50.0)	0.9 (0.3 – 2.3)	0.79
Sepsis (bacteremia) not related to meningitis episode	11 (36.7)	18 (47.4)	0.6 (0.2 – 1.7)	0.38
Severe retinopathy of prematurity (stage 3 or more) ††	8/27 (29.6)	9/34 (26.5)	1.2 (0.4 – 3.6)	0.79
Retinal laser therapy for ROP ††	3/27 (11.1)	6/34 (17.6)	0.6 (0.1 – 2.6)	0.48
Any intraventricular hemorrhage	18 (60.0)	22 (57.9)	1.1 (0.4 – 2.9)	0.86
Severe IVH (grade III or IV)	13 (43.3)	16 (42.1)	1 (0.4 – 2.8)	0.92
Periventricular leukomalacia	10 (33.3)	12 (31.6)	1.1 (0.4 – 3)	0.88
Length of stay at tertiary site	81 ± 58	93 ± 62	1 (1 – 1)	0.42
Death in the NICU	6 (20.0)	7 (18.4)	1.1 (0.3 – 3.7)	0.87

* Comparison by univariate unconditional logistic regression. The dependent variable is Meningitis - definite meningitis is coded as 1 and possible meningitis as 0. The independent variables are the Characteristics with 0 coded as exposure/outcome not present and 1 as exposure/outcome present.

† Plus – minus values are means ± SD; frequencies are no. (%)
‡ A total of 17 mothers were swabbed for Group B Streptococcal status
§ Significant difference between groups ($p < 0.05$)
‖ Four infants in the definite meningitis group and five infants in the possible meningitis group died prior to 36 weeks, and thus could not by definition develop chronic lung disease. These infants were coded "died" and were not included in the analysis.
†† Three infants in the definite meningitis group and five infants in the possible meningitis group died prior to 32 weeks, and thus did not have retinal examinations done. These infants were coded "died" and were not included in the analysis.

TABLE 4.2. Clinical manifestations of meningitis and concurrent conditions associated with meningitis * †

Characteristic	Definite meningitis (N = 30)	Possible meningitis (N = 38)	OR (95% CI)	p
Late-onset meningitis	27 (90.0)	35 (92.1)	0.8 (0.1 – 4.1)	0.76
Central nervous system manifestations	21 (70.0)	25 (65.8)	1.2 (0.4 – 3.4)	0.71
Seizures	17 (56.7)	12 (31.6)	2.8 (1.0 – 7.7)	0.04 ‡
Temperature instability	11 (36.7)	11 (28.9)	1.4 (0.5 – 3.9)	0.50
Respiratory symptoms	23 (76.7)	28 (73.7)	1.2 (0.4 – 3.6)	0.78
Apnea and bradycardias	19 (63.3)	29 (76.3)	0.5 (0.2 – 1.5)	0.25
Gastrointestinal symptoms	17 (56.7)	21 (55.3)	1.0 (0.4 – 2.8)	0.91
Cardiovascular symptoms	16 (53.3)	21 (55.3)	0.9 (0.3 – 2.4)	0.87
Glucose instability	6 (20.0)	2 (5.3)	4.5 (0.8 – 24.2)	0.08
Associated necrotizing enterocolitis with meningitis	4 (13.3)	5 (13.2)	1.0 (0.2 – 4.2)	0.98
Associated hypotension with meningitis	13 (43.3)	14 (36.8)	1.3 (0.5 – 3.5)	0.59
Central intravascular catheter present at the time of meningitis	16 (53.3)	30 (78.9)	0.3 (0.1 – 0.9)	0.03 ‡
Ventricular reservoir present at the time of meningitis	6 (20.0)	4 (10.5)	2.1 (0.5 – 8.3)	0.28
Hyponatremia at the time of meningitis	13 (43.3)	9 (23.7)	2.5 (0.9 – 7)	0.09

* Comparison by univariate unconditional logistic regression. The dependent variable is Meningitis - definite meningitis is coded as 1 and possible meningitis as 0. The independent variables are the Characteristics (clinical manifestations of meningitis or concurrent conditions associated with meningitis) with 0 coded as characteristic not present and 1 as characteristic present.

† Frequencies are no. (%)

‡ Significant difference between groups ($p < 0.05$)

Causative organisms cultured from CSF and blood are presented in TABLE 4.3. Coagulase-negative staphylococcus (23 infants) and *E. coli* (10 infants) were the most common pathogens isolated overall. Coagulase-negative staphylococcus (21 infants) and *C. albicans* (9 infants) were the most common organisms isolated amongst infants with a birth weight < 1250g, and *E. coli* (6 infants) and GBS (4 infants) amongst the infants with a birth weight $\geq$ 1250g. In infants with early-onset meningitis, *E. coli* (2 infants), *Listeria monocytogenes* (1 infant), non typeable *Haemophilus influenzae* (1 infant) and no organism (2 infants) were isolated.

Amongst infants with meningitis and/or sepsis with coliforms (*E. coli* and *Klebsiella spp*), ampicillin resistance was found in 11 (79%) of the 14 isolates. Amongst the 23 infants with coagulase-negative staphylococcal meningitis and/or sepsis, 17 (74%) of the isolates were resistant to oxacillin.

Blood cultures were negative in 20 of the infants at the time they were diagnosed with meningitis (29%), 17 of whom had concurrent positive CSF cultures (CONS [N = 9], *C. albicans* [N = 2], *E. coli* [N = 2], *U. urealyticum* [N = 2], Clostridium not perfringens [N = 1], and *Bacteroides fragilis* [N = 1]). Three infants had negative blood and CSF cultures, but fit the criteria for possible meningitis based on elevated CSF WCC and pretreatment with antibiotics in one infant, and elevated CSF WCC with bloody taps and treated with antibiotics for > 72 hours for possible sepsis in two infants.

CSF and blood laboratory investigations at the time of initial diagnosis and peak CSF white cell count (WCC) and chemistry are presented in TABLE 4.4. Newborns with definite meningitis were more likely to have a higher peak CSF WCC, a lower CSF glucose level and a positive gram stain.

TABLE 4.3. Organisms cultured from cerebrospinal fluid and blood of infants with meningitis *

	Definite meningitis (N = 30)	Possible meningitis (N = 38)		Totals
Isolate	**CSF**	**CSF**	**CSF and blood †**	**CSF and blood**
Staphylococci				
Coagulase-negative staphylococcus	3 (10.0)	16 (42.1)	20 (52.6)	23 (33.8)
Staphylococcus aureus	1 (3.3)	-	-	1 (1.5)
Coliforms				
Escherichia coli	9 (30.0)	1 (2.6)	1 (2.6)	10 (14.7)
Klebsiella spp.	1 (3.3)	2 (5.3)	3 (7.9)	4 (5.9)
Streptococci				
Group B streptococcus	5 (16.7)	-	2 (5.3)	7 (10.3)
Enterococcus faecalis	2 (6.7)	2 (5.3)	2 (5.3)	4 (5.9)
Streptococcus bovis	1 (3.3)	-	-	1 (1.5)
Other				
Candida spp	3 (10.0)	5 (13.2)	6 (15.8)	9 (13.2)
Ureaplasma urealyticum	2 (6.7)	-	-	2 (2.9)
Listeria monocytogenes	1 (3.3)	-	-	1 (1.5)
Bacteroides fragilis	1 (3.3)	-	-	1 (1.5)
Clostridium not perfringens	1 (3.3)	-	-	1 (1.5)
Non typeable *Haemophilus influenzae*	-	-	1 (2.6)	1 (1.5)
No organism cultured †	-	12 (31.6)	3 (7.9)	2 (2.9)
	30 (100.0)	38 (100.0)	38 (100.0)	68 (100.0)

* Frequencies are no. (%) within the group

† The 12 infants whose CSF cultures did not identify an organism were reclassified by organism cultured from blood

TABLE 4.4. Cerebrospinal fluid white cell counts, gram stain and chemistry, and blood white cell count, platelet count and serum glucose findings of infants with meningitis *

	Definite meningitis (N = 30)		Possible meningitis (N = 38)		
	n	Mean ± SD	n	Mean ± SD	p
Laboratory values at initial diagnosis of meningitis					
CSF WCC (x 10^6/L)	25	896 ± 1594	28	571 ± 1564	0.46 †
CSF protein (g/L)	23	6.2 ± 3.8	31	6.2 ± 9.2	0.99 †
CSF glucose (mmol/L)	23	1.7 ± 1.1	31	3.5 ± 2.1	<0.01 †‡
Peripheral WCC (x 10^9/L)	28	15 ± 9	35	17 ± 11	0.46 †
Peripheral platelet count (x 10^9/L)	24	207 ± 205	28	152 ± 128	0.24 †
Serum glucose (mmol/L l)	26	5.8 ± 2.9	20	6.5 ± 5.2	0.57 †
Peak CSF laboratory values					
CSF WCC (x 10^6/L)	28	2133 ± 3335	35	491 ± 1413	0.02 †‡
CSF protein (g/L)	27	6.8 ± 4.1	35	6.0 ± 8.6	0.65 †
Lowest CSF glucose (mmol/L)	26	1.3 ± 0.5	36	2.5 ± 1.6	<0.01 †‡
CSF gram stain					
Gram stain positive	30	15 (50)	37	4 (11)	<0.01 §‡

* Plus – minus values are means ± SD; frequencies are no. (%). Not all infants had indicated specimens sent, thus total numbers (n) are reported

† Comparison by t-test

‡ Significant difference between groups ($p < 0.05$)

§ Gram stain positive OR 8.3 (95% CI 2.3 - 29.1)

Section 4.3: Follow-up of premature infants with meningitis and factors associated with prognosis

Of the 68 infants with meningitis, 15 infants died, 7 in the definite meningitis group and 8 in the possible meningitis group (FIGURE 4.1). Amongst infants with definite meningitis, 6 infants died in the NICU from multi-organ failure (N = 1), intracranial bleed (N = 1), respiratory failure (N = 1) and overwhelming sepsis (N = 3), and one infant died after discharge from NICU from respiratory failure. From chart review, four of these seven deaths (57.1%) may have been attributable to meningitis. Amongst infants with possible meningitis, 7 died in the NICU from multi-organ failure (N = 1), intracranial bleed (N = 2), respiratory failure (N = 3) and withdrawal of support (N = 1), and one infant died after discharge from the NICU from respiratory failure. Five of these eight deaths (62.5%) may have been attributed to meningitis.

There were similar numbers of infants lost to follow-up in each group, 2 in the definite meningitis group and 3 in the possible meningitis group (TABLE 4.5 and FIGURE 4.1). Four of the five infants lost to follow-up were > 1250g and ≥28 weeks at birth. Thus 48 survivors who had meningitis, definite or possible, were assessed at 18-months adjusted age. Of these 48 infants, 16 had cerebral palsy (33.3%), 32 had cognitive delay (66.7%), 5 had sensorineural hearing loss (10.4%), 7 had visual loss (14.6%) and 1 had epilepsy (2.1%). Twelve infants had no disability - four infants with definite meningitis and eight infants with possible meningitis. The mean MDI of all infants with meningitis, definite or possible, was 64 with a SD of 17.

Outcomes, death or disability at 18 months, were similar between the two groups (TABLE 4.5). There was no difference in the MDI scores between infants with definite

meningitis (mean ± SD = 66 ± 20; median 60) and possible meningitis (mean ± SD = 63 ± 14; median 62) (TABLE 4.5 and FIGURE 4.2). Infants with a VP shunt in place at 18 months (18 infants in total – 11 in the definite meningitis group and 7 in the possible meningitis group) had lower MDIs compared to infants who did not have a VP shunt (infants with VP shunt 57 ± 13; infants without VP shunt 69 ± 17; p = 0.01) (FIGURE 4.3).

Prognostic variables for adverse outcome (composite death or disability) in the univariate unconditional logistic regression are presented in TABLE 4.6. From the univariate unconditional logistic regression, several variables including birth weight, patent ductus arteriosus, hypotension requiring inotrope support at any time during the NICU stay, VP shunt present at 18 months, respiratory symptoms with episode of meningitis, cardiovascular symptoms with episode of meningitis, hypotension requiring inotrope support at the time of meningitis and central intravascular catheter present at the time of meningitis, were significantly associated with an adverse outcome, and were entered into a multivariate model (TABLE 4.7). The most parsimonious multivariate model predicting an adverse outcome included central intravascular catheter present at time of meningitis and VP shunt present at 18-months (TABLE 4.8).

TABLE 4.5. Neurodevelopmental outcomes at 18-months adjusted age for infants with meningitis

	Definite meningitis (N = 30)	Possible meningitis (N = 38)	OR (95% CI)	p *
Outcome	No/total no. (%)			
Lost to follow-up	2/30 (6.7)	3/38 (7.9)	0.8 (0.1 – 5.3)	0.85
Composite outcome				
Death or disability	24/28 (85.7)	27/35 (77.1)	1.8 (0.5 – 6.7)	0.39
Components				
Death in the NICU	6/30 (20.0)	7/38 (18.4)	1.1 (0.3 – 3.7)	0.87
Death before 18 months	7/28 (25.0)	8/35 (22.9)	1.1 (0.3 – 3.6)	0.84
Any disability	17/21 (81.0)	19/27 (70.0)	1.8 (0.5 – 7.0)	0.40
Cerebral palsy	8/21 (38.1)	8/27 (29.6)	1.5 (0.4 – 4.9)	0.54
Cognitive delay (MDI < 70)	14/21 (66.7)	18/27 (66.7)	1 (0.3 – 3.3)	1
Severe cognitive delay (MDI < 55)	10/21 (47.6)	11/27 (40.7)	1.3 (0.4 – 4.2)	0.63
Hearing loss	4/21 (19.0)	1/27 (3.7)	6.1 (0.6 – 59.5)	0.12
Visual loss	3/21 (14.3)	4/27 (14.8)	1 (0.2 – 4.8)	0.96
Epilepsy	0	1/27 (3.7)	0	1
Other outcomes at 18 months				
Ventriculoperitoneal shunt at 18 months	11/21 (52.4)	7/27 (25.9)	3.1 (0.9 – 10.6)	0.07
Multiply disabled †	7/21 (33.3)	9/27 (33.3)	1 (0.3 – 3.3)	1
MDI (mean ± SD)	65.76 ± 20.11	63.37 ± 14.28		0.63 ‡

* Comparison by univariate unconditional logistic regression. Independent variable is Group (definite meningitis coded as 1 and possible meningitis as 0)

† Child affected by two or more disabilities

‡ Comparison by t-test

FIGURE 4.2. Bayley Mental Developmental Index (MDI) scores categorized by standard deviation for infants with definite meningitis (N=30), possible meningitis (N=38). Bayley scale scores provide an MDI with a mean of 100 and SD of 15. Scores less than 70 are > 2SD and scores less than 55 are > 3SD below the mean of standardized testing

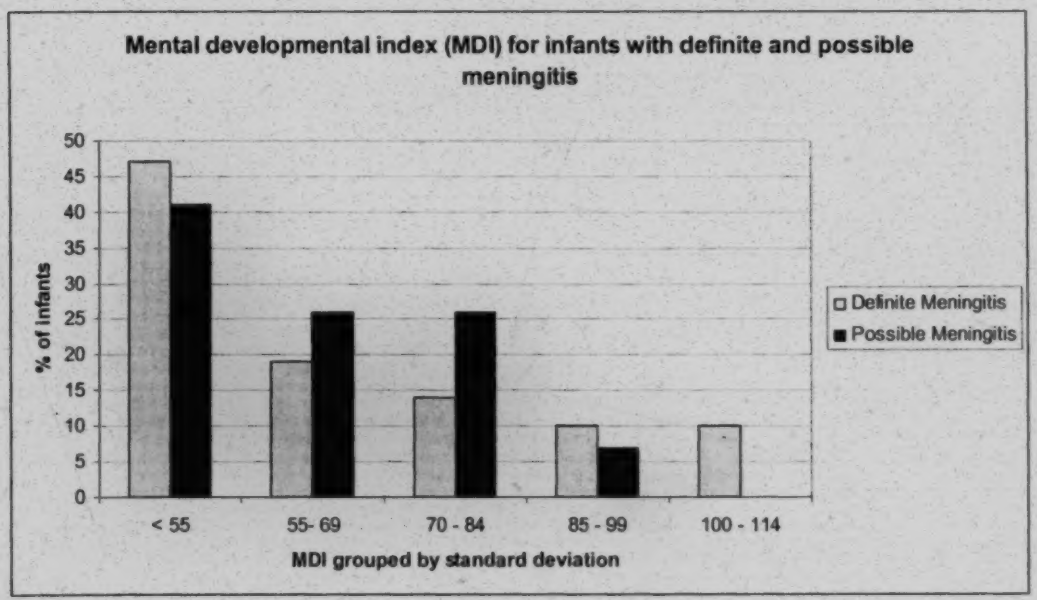


FIGURE 4.3. Boxplot graphs depicting Bayley Mental Developmental Index scores of neonates with definite (N = 30) and possible meningitis (N = 38), selecting for infants who had a ventriculoperitoneal shunt in place at 18 months (18 infants in total with VP shunt – 11 in the definite meningitis group and 7 in the possible meningitis group)

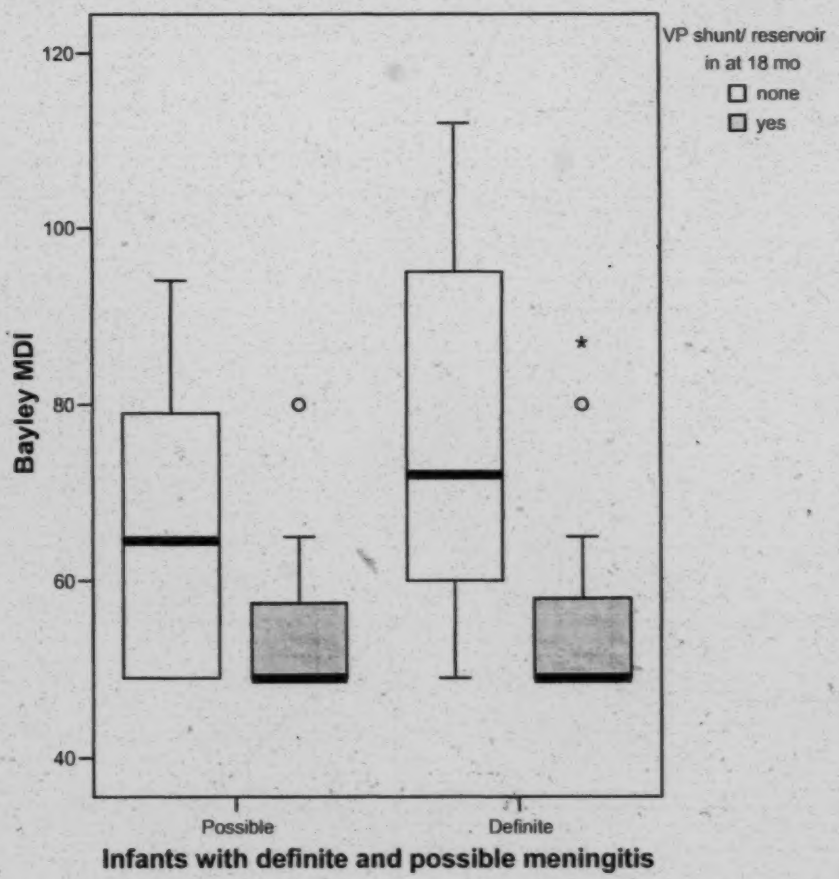


TABLE 4.6. Prognostic variables for adverse outcome (composite death or disability) using univariate unconditional logistic regression of all infants with meningitis, definite meningitis (N = 30) and possible meningitis (N = 38) *

Prognostic variable	**OR**	**95% CI**	**p** †
Definite meningitis	1.8	0.5 - 6.7	0.39
Neonatal and maternal variables			
Birth weight	1	1 – 1	0.02 ‡
Gestational age	0.8	0.7 – 1	0.06
Birth weight < 1250g	1.8	0.5 – 7.2	0.39
Gestational age < 28 weeks	2.4	0.7 – 8.6	0.18
Male sex	0.6	0.2 – 2.1	0.39
Twin or triplet	0.9	0.2 – 5.1	0.93
Intrauterine growth restriction	1.7	0.2 – 15.7	0.62
Outborn	0.4	0.1 – 1.7	0.24
Apgar score 5 minutes	0.7	0.4 – 1.1	0.10
Prolonged rupture of membranes	1.4	0.3 – 5.7	0.67
Maternal fever	2.7	0.3 – 23.3	0.37
Intrapartum antibiotics	1.0	0.3 – 3.7	0.95
Antenatal steroids	1	0.3 – 3.7	0.95
Cesarean section	1.4	0.3 – 5.8	0.67
Respiratory distress syndrome	2.5	0.5 – 11.9	0.25
Hypotension	4.5	1.2 – 17	0.02 ‡
Patent ductus arteriosus	4.1	1.1 – 15.1	0.04 ‡
Chronic lung disease	2.5	0.7 – 9.3	0.17
Doxapram for apnea of prematurity	1	0.3 – 3.4	0.95
Intraventricular hemorrhage	2.6	0.7 – 9.3	0.15
Severe IVH (grade III or IV)	3.1	0.8 – 12.9	0.12
Periventricular leukomalacia	3.2	0.6 – 16.3	0.16
Length of tertiary NICU stay	1	1 – 1	0.11
VP shunt at 18 months	9.8	1.1 – 84.4	0.04 ‡

Table 6 continued on page 77

TABLE 4.6 (cont'd). Prognostic variables for adverse outcome (composite death or disability) using univariate unconditional logistic regression of all infants with meningitis, definite meningitis (N = 30) and possible meningitis (N = 38) *

Prognostic variable	OR	95% CI	p †
Variables associated with meningitis episode			
CNS symptoms	2.2	0.6 – 7.8	0.23
Seizures	1.6	0.4 – 6.2	0.46
Temperature instability	1.4	0.3 – 5.8	0.67
Respiratory distress	7.5	1.9 – 29.7	< 0.01 ‡
Apnea and bradycardias	0.4	0.1 – 2	0.27
Gastrointestinal symptoms	1	0.3 – 3.7	0.98
Cardiovascular symptoms	4.6	1.1 – 19.3	0.03 ‡
Glucose instability	1.5	0.2 – 13.5	0.74
Associated hypotension	9.8	1.2 – 81.4	0.04 ‡
Central intravascular catheter present at time of meningitis	10.9	2.5 – 47.3	< 0.01 ‡
Ventricular reservoir present at time of meningitis	2.4	0.3 – 20.6	0.44
Hyponatremia	6	0.7 – 50.3	0.10
Initial CSF WCC x 10(6)	1	1 –1	0.24
Initial CSF protein (g/l)	1.1	0.9 – 1.4	0.26
Initial CSF glucose (mmol/l)	1.1	0.8 – 1.7	0.52
Peak CSF WCC x 10(6)	1	1 – 1	0.24
Peak CSF protein (mmol/l)	1.2	1 – 1.6	0.07
Lowest CSF glucose (g/l)	1.1	0.7 – 1.7	0.75
Serum WCC x 10(6)	1	0.9 – 1.1	0.62
Serum platelet count x 10(9)	1	1 – 1	0.09
Serum glucose (mmol/l)	0.9	0.8 – 1.1	0.31
Gram stain positive	5.2	0.6 – 43.6	0.13

* Dependent variable is composite adverse outcome (death or disability) – 0 is death or disability not present and 1 is death or disability present. Independent variables are labeled "Prognostic variables" in the table – 0 is no exposure and 1 is exposure.

† Comparison by unconditional logistic regression

‡ Significant difference between groups ($p < 0.05$)

TABLE 4.7 Multivariate analysis using unconditional logistic regression for prognostic variables for composite adverse outcome (death or disability) at 18 months amongst all neonates with meningitis [definite meningitis (N = 30) and possible meningitis (N = 38)]

Predictive variable	**OR**	**95% CI**	**p ***
Overall model			<0.01 †
Birth weight	1	1 – 1	0.94
Hypotension	2.2	0.1 – 33	0.56
Patent ductus arteriosus	0.9	0.1 – 9.5	0.90
Ventriculoperitoneal shunt at 18 months	60.4	2.4 – 1521	0.01 †
Respiratory distress at the time of meningitis	2.8	0.1 – 53.9	0.50
Cardiovascular symptoms at the time of meningitis	1	0.1 – 13.0	1
Associated hypotension at the time of meningitis	5.1	0.1 – 189	0.37
Central line present at time of meningitis	26.7	1.3 – 533	0.03 †

* Comparison by unconditional logistic regression – variables from the univariate analysis with $p < 0.05$ were included

† Significant association ($p < 0.05$)

TABLE 4.8. Most parsimonious multivariate model predictive of composite adverse outcome (death or disability) at 18 months amongst all neonates with meningitis [definite meningitis (N = 30) and possible meningitis (N = 38)]

Predictive variable	**OR**	**95% CI**	**p ***
Overall model			<0.01 †
Ventriculoperitoneal shunt at 18 months	52	2.9 – 943	<0.01 †
Central line present at time of meningitis	50.6	4.7 – 548	<0.01 †

* Comparison by unconditional logistic regression – variables from the univariate analysis with $p < 0.05$ from the full multivariate model were included for analysis

† Significant association ($p < 0.05$)

Section 4.4: Infecting pathogen and outcomes

As CONS and the coliforms (*E.coli* and *Klebsiella spp*) were the predominant bacterial isolates, comparison of outcomes was made between these infants (TABLE 4.8). Although infants with CONS meningitis were smaller in gestation and birth weight, there was no difference in outcomes.

Candida meningitis was seen only in infants < 1000g and ≤26 weeks gestation at birth. Of nine infants with Candida meningitis, 8 infants had adverse sequelae: death (N = 3) or disability (N = 5). Of the infants with disability, four were multiply disabled with two or more disabilities and all five had cognitive delay.

U. urealyticum meningitis was seen in 3 patients (a singleton male and set of twin girls), but only two infants are included in our analysis as one of the twins had another episode of meningitis prior to the culture of *U. urealyticum* with CONS. All three infants were < 1000g and ≤26 weeks gestation at birth. Meningitis was suspected by persistently elevated CSF white cell counts. The organism was difficult to detect by culture and was difficult to eradicate, persisting in the CSF for 4 weeks to 3 months. The twins had severe intraventricular bleeds necessitating ventricular reservoir insertion in the NICU and later shunt dependent hydrocephalus at 18 months. In long-term follow-up, the singleton male had no disabilities, but the twins both had severe cognitive delay and one twin also had cerebral palsy and visual loss.

TABLE 4.9. Comparison of outcomes at 18-months adjusted age for infants with meningitis due to coagulase-negative staphylococcus (N = 14) and coliforms (*E. coli* and *Klebsiella spp*) (N = 23) *

	Coliform meningitis	CONS meningitis	OR (95% CI)	p
Birth weight (grams)	1279 ± 640	842 ± 261		0.03 †‡
Gestational age (weeks)	28.4 ± 3.5	25.7 ± 1.5		0.02 †‡
Death in NICU	5/14 (35.7%)	4/23 (17.4)	2.64 (0.57 - 12.25)	0.22 §
Lost to follow-up	0	1/19 (5.3)		
Composite outcome				
Death or disability	11/14 (78.6%)	18/22 (81.8)	0.82 (0.15 - 4.35)	0.81 §
Components				
Death before 18 months	5/14 (35.7)	5/22 (22.7)	1.89 (0.43 - 8.30)	0.40 §
Cerebral palsy	2/9 (22.2)	7/17 (41.2)	0.41 (0.07 - 2.58)	0.34 §
Cognitive delay (MDI < 70)	5/9 (55.6%)	13/17 (76.5)	0.39 (0.07 - 2.16)	0.28 §
Severe cognitive delay (MDI < 55)	4/9 (44.4)	8/17 (47.1)	0.90 (0.18 - 4.56)	0.90 §
Hearing loss	2/9 (22.2)	0		
Visual loss	0	4/17 (23.5)		
Epilepsy	0	1/17 (5.9)		
Other outcomes at 18 months				
Ventriculoperitoneal shunt at 18 months	4/9 (44.4)	7/17 (41.2)	1.14 (0.22 - 5.84)	0.87 §
Multiply disabled ‡	3/9 (33.3)	7/17 (41.2)	0.71 (0.13 - 3.87)	0.70 §
MDI	67.89 + 19.91	59.65 + 12.13		0.28 †

* Plus – minus values are means ± SD; frequencies are no. (%)
† Comparison by t-test
‡ Significant difference ($p < 0.05$)
§ Comparison by unconditional logistic regression. Coagulase-negative staphylococcus is coded as 0 and coliforms are coded as 1.

Chapter 5

Discussion and Conclusions

Section 5.1: Introduction

This study was undertaken to determine if meningitis in premature neonates is associated with adverse sequelae in early childhood. Using a hospital-based, inception cohort design, all infants with gestational age ≤36 weeks who were diagnosed with meningitis in the NICU were identified. Two comparisons were undertaken.

The first comparison was between infants with birth weight < 1250g who had definite meningitis in the NICU [cases] and infants who had no meningitis throughout their NICU stay [controls]. A nested matched case control design was used to ascertain risk characteristics predisposing to meningitis. These infants were followed to compare outcomes, survival and neurodevelopmental sequelae, at 18-months adjusted age between infants with meningitis and controls. Maternal and neonatal characteristics and complications were examined to determine if any of these variables were predictive of adverse outcome [death or disability] and cognitive ability (MDI).

The second comparison was between infants ≤36 weeks gestational age with definite meningitis and possible meningitis to ascertain differences in demographic features, maternal and neonatal complications, clinical characteristics of the episode of meningitis, responsible pathogens, and laboratory findings. These infants were followed to 18-months to compare outcomes. Neonatal demographic features, maternal and neonatal complications, clinical characteristics of the episode of meningitis, responsible pathogen and laboratory findings were examined to ascertain any prognostic variables for adverse outcome (composite death or disability).

These findings add to the very few studies directly focusing on the specific consequences of meningitis in premature [≤36 weeks], particularly very low birth weight infants [VLBW < 1500g] (Perlman, Rollins et al. 1992; Doctor, Newman et al. 2001; Stevens, Eames et al. 2003).

Section 5.2: Newborns with birth weight < 1250g

5.2.1: Epidemiology of meningitis in infants with birth weight < 1250g from the Northern Alberta NICUs

Over the 14 year period, 1990 to 2003, the incidence of meningitis amongst infants < 1250g at 30 per 1000 live births was much higher than term infants (Holt, Halket et al. 2001; Grupo 2002; Persson, Trollfors et al. 2002) but comparable to other studies involving VLBW infants (Doctor, Newman et al. 2001). (The incidence of meningitis amongst infants ≤36 weeks could not be calculated as not all these infants, with or without meningitis, may have been admitted to the NICUs.)

The case fatality rate of meningitis in this cohort of premature infants < 1250g was 27%. This rate is higher than in term infants (Harvey, Holt et al. 1999; Klinger, Chin et al. 2000; Holt, Halket et al. 2001), but comparable to VLBW infants (Doctor, Newman et al. 2001). It was often difficult to determine whether death in the infants with meningitis was attributable to meningitis or its complications. The causes of death included severe intracranial hemorrhage, multi-organ failure, overwhelming sepsis and respiratory failure, all of which may have been associated with sepsis and/or meningitis.

Section 5.2.2: Factors associated with meningitis

Although meningitis occurs more commonly during the neonatal period than at any other time of life, it is still a fairly rare disease and thus a case control study design is well suited to evaluate a range of potential factors associated with causation between affected and non-affected neonates. All cases were selected according to strict diagnostic criteria for definite meningitis. Control infants were treated in the same tertiary NICU

and were matched to cases by year of birth (± 1 year) to ensure that any changes in neonatal care would be consistent between cases and controls.

In the only study in the literature focusing on meningitis in VLBW infants and their long term outcomes, Doctor compares infants with meningitis with all other infants admitted to the same NICU during the same time period (Doctor, Newman et al. 2001). Survivors of neonatal meningitis had more major neurologic abnormalities and subnormal MDI (MDI < 70) even after controlling for birth weight, IVH, CLD and social factors. The effect of meningitis on neurologic and developmental outcomes in Doctor's study is difficult to interpret as the infants with meningitis had a significantly lower gestational age and birth weight and more neonatal complications such as RDS, sepsis, NEC, CLD, periventricular hemorrhage, PVL and hydrocephalus compared to infants without meningitis.

In order to improve upon Doctor's study, matched controls were used in this study to eliminate the effect of variables which were thought to be important confounders at two levels. Firstly, lower gestational age, lower birth weight, male sex and multiple pregnancy are risk factors for developing meningitis Secondly, lower gestational age, lower birth weight, IVH, male sex and multiple pregnancy are related to meningitis (exposure) and are also risk factors for mortality and adverse neurodevelopmental outcomes (disease) (Aziz, Vickar et al. 1995; Hack, Wilson-Costello et al. 2000; Vohr, Wright et al. 2000; Wood, Costeloe et al. 2005). Matching in this study was rigorous, particularly for birth weight, gestational age and IVH. Analysis was done by matched case control clusters (case, control 1, control 2) by conditional logistic regression for ascertaining risk characteristics predisposing to meningitis (nested case control study)

and by unconditional logistic regression in matched clusters for determining outcomes with or without meningitis (follow-up study).

This study found that a decreased maternal exposure to antenatal steroids and the presence of CLD were associated with an increased risk of developing meningitis. These variable have not previously been shown to be important risk factors predisposing to meningitis (de Louvois 1994; Fanaroff, Korones et al. 1998; Volpe 2000; Klein 2001; Stoll, Hansen et al. 2002). Intuitively, infants who have not benefited from antenatal exposure to steroids would require prolonged ventilation for respiratory distress syndrome (Crowley 2000) and thereby, indirectly, be at higher risk of developing CLD as well as meningitis. This explanation cannot be confirmed as data regarding number of days of mechanical ventilation between infants with and without meningitis were unavailable. A further difficulty with trying to explain the association between CLD and meningitis is the temporal sequence between exposure and disease in a case control design. An infant with CLD may require a prolonged hospital stay with more invasive procedures such as ventilation, predisposing the infant to sepsis and meningitis. Chronic lung disease, on the other hand, could be a consequence of sepsis and meningitis. These two variables, maternal antenatal corticosteroid exposure and CLD, thus are interesting observations, but cannot readily be explained and have not previously been described as risk characteristics for meningitis.

Other maternal and intrapartum factors predisposing to sepsis such as prolonged rupture of membranes or chorioamnionitis were not associated with meningitis in this study. These factors have been associated with sepsis and meningitis, particularly with early-onset disease in other studies (Overall 1970; de Louvois 1994; Klein 2001). Most

episodes of meningitis in this study were late-onset disease [18/19 infants (94.7%)] and thus the impact of intrapartum complications may have been less important. Also, important clinical information may have been missed from a retrospective chart review. The definition of chorioamnionitis in this study was clinical rather than histological, thus women with subclinical chorioamnionitis may have been misclassified, underestimating the impact of chorioamnionitis on the development of sepsis and meningitis. Unlike in other studies (Stoll, Hansen et al. 2002), duration of hospitalization in a tertiary care centre was not different in infants with and without meningitis in my study.

Section 5.2.3: Survival and neurodevelopmental outcomes

When comparing infants with and without meningitis with respect to outcome, there was an alarming increase in mortality (36.8% vs. 10.5%), any disability (75.0% vs. 44.1%) and composite outcome, death and disability (84.2% vs. 50.0%) at 18-months adjusted age in infants < 1250g with meningitis. Disability rates of cerebral palsy (41.7% vs. 8.8%), moderate cognitive delay (58.3% vs. 38.2%), sensorineural hearing loss (16.7% vs. 5.9%) and visual loss (16.7% vs. 5.9%) were increased in infants with meningitis compared to control infants. Epilepsy was not seen in either group. The mean MDI was subnormal (<70) but similar in infants with and without meningitis (MDI 69 vs. 71); however, infants who required a VP shunt at 18-months in either group, had a lower MDI compared to infants who did not require a VP shunt (MDI 56 vs. 72).

These neurodevelopmental outcomes are worse than those reported by Doctor in other VLBW infants with meningitis. They reported that 51% of VLBW infants meningitis had a major neurologic abnormality with a mean MDI of 78 (Doctor, Newman et al. 2001). Moreover, these outcomes are worse than those reported for extremely

preterm infants in other populations (Hack, Wilson-Costello et al. 2000; Vohr, Wright et al. 2000; Wood, Costeloe et al. 2005). There are several explanations for the poorer outcomes of the infants with meningitis noted in this study compared to Doctor's: (1) infants included in this study were < 1250g at birth (Doctor included infants < 1500g), (2) infants in this study were slightly smaller at birth, had a slightly lower gestational age, and had more complications such as CLD, PVL and hydrocephalus than the infants in Doctor's study, (3) infants in this study had definite meningitis whereas Doctor included all infants with a positive CSF culture, some of whom may have actually had a contaminant grow in CSF rather than had true meningitis .

Section 5.2.4: Factors associated with prognosis

In this present study, meningitis and severe IVH were the two variables found to be the strongest predictors for adverse outcome, death or disability. In large cohort studies, Hack and Stoll have found that meningitis is a predictor of neurodevelopmental disability (Hack, Wilson-Costello et al. 2000; Stoll, Hansen et al. 2004). Severe IVH has been shown in many studies, including a large province-based study from Alberta (Aziz, Vickar et al. 1995), to be associated with adverse outcome. Hypotension, severe ROP and PVL were other variables predictive of adverse outcome. These results corroborate findings from previous studies in VLBW infants in which all these variables have been associated with adverse outcome (Aziz, Vickar et al. 1995; Goldstein, Thompson et al. 1995; Murphy, Hope et al. 1997; Perlman 1998; Hack, Wilson-Costello et al. 2000; Martens, Rijken et al. 2003; Schmidt, Asztalos et al. 2003; Stoll, Hansen et al. 2004).

Shunt-dependent hydrocephalus post-meningitis was a common complication in this study and was predictive of later cognitive ability (B coefficient -12.73; SE 6.22; p =

0.05). Ventriculitis, progressive ventriculomegaly, thalamic echodensities and late-onset IVH have been seen on serial head ultrasound scans of VLBW infants with meningitis (Perlman, Rollins et al. 1992). Of these, ventriculitis and progressive ventriculomegaly were associated with the need for placement of a permanent VP shunt. In this present study, of the 8 infants with meningitis who required a ventricular reservoir for hydrocephalus in the NICU, 2 infants died in the NICU and 4 infants required insertion of a VP shunt. In other studies, extremely preterm infants with acquired progressive hydrocephalus requiring VP shunting (usually as a complication of IVH with posthemorrhagic hydrocephalus) also have poorer outcomes (Davis, Tooley et al. 1987; Etches, Ward et al. 1987; Levy, Masri et al. 1997; Murphy, Inder et al. 2002).

Section 5.3: Meningitis in premature neonates ≤36 weeks gestation – comparison of infants with definite and possible meningitis

Section 5.3.1: Clinical manifestations, responsible pathogens and laboratory findings

Clinicians will often diagnose meningitis in premature infants even though there may not be classical evidence of meningitis in CSF findings. In this study, infants were classified as having definite or possible meningitis according to preset criteria so as to ensure uniformity and degree of certainty of diagnosis of meningitis and to compare differences in clinical manifestations and outcomes between infants with definite and possible meningitis.

The clinical manifestations of infants with definite and possible meningitis were non-specific. Most infants presented with central nervous system manifestations (lethargy, hypotonia, irritability), respiratory symptoms (respiratory distress, increasing oxygen requirements, need for reintubation), and apneas or bradycardias. Infants with definite meningitis were more likely to develop seizures as a manifestation of meningitis and infants with possible meningitis were more likely to have a central intravascular catheter in place at the time of diagnosis of meningitis. Infants with possible meningitis were slightly smaller and less mature than infants with definite meningitis, perhaps accounting for a higher prevalence of central intravascular catheters in this group of infants.

In this NICU population, meningitis appeared to be a nosocomial disease as most infants had late-onset infection caused by CONS (34%), particularly amongst infants < 1250g. Infants with "meningitis" thought to be due to a contaminant with a common skin

isolate [defined as a positive CSF culture with a common skin contaminant with a normal CSF white cell count and treated for < 72 hours with antibiotics with no recurrence, or growth of the organism in liquid media only], were excluded from the analysis. These findings reflect other studies where CONS is the most common pathogen involved in late-onset sepsis and meningitis in VLBW infants (Doctor, Newman et al. 2001; Stoll, Hansen et al. 2002).

Oxacillin-resistant strains of CONS were seen in 74% of the isolates. Ampicillin-resistant strains of coliforms (*Escherichia coli* and *Klebsiella* spp) were seen in 79% of isolates. The majority of these infants had late-onset meningitis. This study cannot assess whether the antibiotic resistance seen reflects local patterns in neonatal, maternal or ambulatory populations. Data were available on maternal intrapartum antibiotic exposure, but not the duration of antibiotics used.

Of note, up to one-third of the infants diagnosed with meningitis based on CSF cultures had concurrent negative blood cultures, in keeping with other reports (Visser and Hall 1980; Doctor, Newman et al. 2001; Stoll, Hansen et al. 2004), further emphasizing the need to do a lumbar puncture in any premature neonate with suspected late-onset sepsis. Even with the remote possibility of a traumatic lumbar puncture leading to secondary meningitis (Hristeva, Booy et al. 1993), if the co-occurrence of meningitis in a septic preterm neonate approaches 25% (Klein 2001), the performance of a lumbar puncture as part of the complete evaluation for infection can be justified.

On the whole, an appropriate inflammatory spinal fluid response was evident with elevated CSF WCCs, elevated CSF protein levels and low CSF glucose levels. Standard deviations were wide, however, and overlapped with normal ranges. This has been

observed in other studies involving premature and VLBW infants (Sarff, Platt et al. 1976; Gruskay, Harris et al. 1989; Rodriguez, Kaplan et al. 1990). Neonates with definite meningitis were more likely to have a higher peak CSF WCC, lower CSF glucose levels and positive gram stain. These findings are reflective of our preset criteria for definite and possible meningitis. Overall, peripheral white cell counts and platelet counts were not overtly suggestive of an infectious/inflammatory process, which is confirmed in other reports (Bonadio, Smith et al. 1992; Omar, Salhadar et al. 2000; Malik, Hui et al. 2003), however, absolute neutrophil or band counts were not specifically explored. The need to initiate and continue with antimicrobial therapy could not be ascertained solely on CSF or blood count parameters, but needed to be evaluated in the total context of the clinical picture. Low CSF WCC and high protein levels have been shown to be predictive of survival (Fitzhardinge, Kazemi et al. 1974; McCracken and Mize 1976; Franco, Cornelius et al. 1992); this was not borne out in our study.

Section 5.3.2: Survival, neurodevelopmental outcomes and factors associated with prognosis

This study highlights some of the problems associated with follow-up of an uncommon and potentially fatal disease. Although it spanned a 14 year period (1990 to 2003), only 68 premature infants $\leq$36 weeks gestational age were identified with meningitis in the NICU. Of these 68 infants, 15 infants died and 5 were lost to follow-up; thus only 48 survivors were assessed at 18-months adjusted age. Cerebral palsy (33.3%), cognitive delay (66.7%), sensorineural hearing loss (10.4%), visual loss (14.6%) and epilepsy (2.1%) were diagnosed in the 48 survivors. The mean MDI was subnormal (64 ± 17) amongst all infants with meningitis. The revised Bayley Scales of Infant

Development II (BSID-II) (Bayley 1993) was used in the Neonatal Follow-up clinic from 1993 on, but only two infants (both with possible meningitis) were born in 1990 thus the vast majority of infants were tested using the BSID-II. Given that many infants had an MDI < 70 associated with other neurosensory deficit, the outcomes of these infants would remain important markers of future risk of academic, motor and social functioning difficulties, and would not be affected by the revision of the Bayley scales.

An important finding from this study, using the comparison between infants with definite and possible meningitis, was that regardless of the certainty of diagnosis, a preterm neonate diagnosed with meningitis had a high risk of death or disability.

Predictive models of adverse outcome of neonatal bacterial meningitis have been developed for term infants (Bortolussi, Krishnan et al. 1978; Klinger, Chin et al. 2000). There are no similar studies available for preterm infants with meningitis. In this study, shunt-dependent hydrocephalus at 18-months and a central intravascular catheter present at the time of meningitis were predictive for adverse outcome but with wide confidence intervals. These variables, especially progressive hydrocephalus post-meningitis, may be used cautiously by neonatologists to counsel parents on further management and on anticipating special needs for their child.

The infecting pathogen did not appear to influence mortality and neurodevelopmental morbidity. The two most common organisms identified in this study were CONS and coliforms (*E. coli* and *Klebsiella spp*). Infants with coliform meningitis were more mature in gestational age and larger in birth weight than infants with CONS, but outcomes were similar between the two groups in terms of survival and neurodevelopmental disability. These findings are in contrast to studies which show

adverse outcomes associated with gram negative bacillary meningitis (Fitzhardinge, Kazemi et al. 1974; Franco, Cornelius et al. 1992; Unhanand, Mustafa et al. 1993; de Louvois 1994), but in agreement with others which show no difference (Doctor, Newman et al. 2001; Stevens, Eames et al. 2003).

Candida meningitis was predominantly seen in infants < 1000g and ≤26 weeks gestation at birth and was associated with death (38%) and disability (55%) amongst affected neonates. These findings reflect other reports of invasive candidiasis being an important cause of nosocomial infection in VLBW infants associated with high mortality and morbidity (Faix 1984; Lee, Cheung et al. 1998; Fernandez, Moylett et al. 2000; El-Masry, Neal et al. 2002).

All three infants with *U. urealyticum* were extremely premature, ≤26 weeks gestation and < 1000g at birth. As has been noted in other studies, the most striking feature was the chronicity of the central nervous system infection with concurrent negative blood cultures (Waites, Rudd et al. 1988; Hentschel, Abele-Horn et al. 1993; Waites, Crouse et al. 1993). The infants had elevated CSF WCCs persisting for weeks up to three months. The organism was difficult to isolate on culture and difficult to eradicate despite use of several concurrent antibiotics. In long-term follow-up, two of the infants had shunt dependent hydrocephalus at 18 months, severe cognitive delay and one infant also had cerebral palsy and visual loss.

Section 5.4: Strengths and limitations of this study

There are several strengths of this study. The criteria for a diagnosis of meningitis were rigorous. There was a low rate of losses to follow-up. Standardized assessment was done at 18-24 months adjusted age by a multidisciplinary team familiar with neonatal follow-up. Confounding variables for developing meningitis and for adverse outcome: gestational age, birth weight, IVH, sex and multiple pregnancy were controlled by matching infants < 1250g for these variables.

Limitations of this study include its retrospective design and small sample size. In the nested case control study, amongst the 19 infants < 1250g defined as having definite meningitis, mortality was 37% (7/19) and no infants were lost to follow-up, thus only 12 survivors were assessed in comparison to control infants. Although a sample size of 12 survivors was required in order to detect a mean difference in MDI between infants with and without meningitis, the small numbers are reflected in the artificially high and excessively wide confidence intervals obtained with uni- and multivariate analyses.

Cases of meningitis may have been missed because only neonates who underwent a lumbar puncture were considered. An unknown number of patients who died from sepsis and who did not have either a lumbar puncture or an autopsy may have been excluded, underestimating the incidence of meningitis and mortality rate. In other children who survived, meningitis is unlikely to remain subclinical with inadequate treatment. All charts of infants who were thought to have had meningitis in the NICU were reviewed, and only those infants who clinically and diagnostically were thought to have meningitis and who were treated for meningitis, were included.

Family socioeconomic status and maternal education level have previously been shown to be related to neurodevelopmental outcome in preterm infants (Hack, Wilson-Costello et al. 2000; Vohr, Wright et al. 2000), but were not available for all infants, and thus was not used as part of the analysis. These study results are applicable only to preterm infants treated at tertiary NICU centres. Nevertheless, this data contributes to the paucity of information available on the consequences of meningitis amongst premature infants with a focus on neonates < 1250g – the population at highest risk of developing meningitis.

Chapter 5.5: Conclusion

In summary, this inception hospital-based cohort study involving premature infants admitted to a neonatal intensive care unit demonstrates an association between neonatal meningitis and increased risk of mortality and poor neurodevelopmental outcome in early childhood. Post-meningitis hydrocephalus requiring ventriculoperitoneal shunting was a common complication and was an important prognostic variable for adverse neurodevelopmental outcomes and cognitive ability. Follow-up and comprehensive developmental assessment is essential for premature infants who develop meningitis in the NICU.

Meningitis in preterm infants is predominantly a nosocomial infection. Coagulase-negative staphylococcus and *E. coli* were the pathogens most commonly isolated. Strategies to reduce the high rates of infection in these infants such as careful handwashing, fastidious management of central intravascular catheters and quality improvement models, are likely to have the most impact on decreasing the adverse sequelae related to meningitis. This study confirms the importance of performing a lumbar puncture in any infant with suspected late-onset sepsis.

A subsequent study involving multiple centres would be desirable to further document the outcomes of premature neonates with meningitis, in particular very low birth weight infants, and to ascertain predictive variables for outcome with greater statistical confidence.

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Appendix 1: Royal Alexandra Hospital NICU datasheet

_____ NNRL
_____ Respiratory
_____ Physician
_____ Secretary

Return to NICU, Room 5027 *please initial when complete*

RAH - NICU DATABASE ADMISSION FORM Postal Code: _____

Hospital ID#: _____ Name: _____

Baby PHN _____ Readmission _____ (Y/N) Gender _____(M/F/A) Date of Birth: _____ (y/m/d)

Time of Birth:_____ Birthweight _____ Multiple _____ of _____

Admission Date _____ (y/m/d) Age at Admission _____ (hr.) (if<48hr) _____ (days) (>2 days)

Admission Weight _____ Head Circumference _____ cm Length _____ cm

Apgars 1 min _____ 5 min _____ 10 min_____

Meconium in fluid _____ Voided in CR _____ Passed meconium in CR _____

Cord Gas: Arterial _____ Venous pH _____ Base Excess _____

Resuscitative Measures/Drugs: _____

Referring Physician: _____ Delivery Physician: _____ Infant's Physician: _____

Transport (circle one): Inborn Land Air Referring Hospital _____ Province _____

Referral Reason: ECMO _____ Cardiac _____

Admission BP: Systolic Diastolic Mean
Non-invasive _____
Invasive _____

Admission Temperature _____ Gestational Age by Exam: _____ *(Dubowitz/Ballard)*
Gestational Age by Dates: _____

Fertility/Antepartum Risk Factors IVF Y/N/Unknown Fertility Drugs Y/N/Unknown

- π UTI
- π GBS Negative
- π GBS Positive
- π GBS Unknown
- π Sepsis other than GBS
- π HIV Positive
- π HIV Negative
- π HIV Unknown
- π Polyhydramnios
- π Oligohydramnios
- π Abruptio Placenta
- π Placenta Previa
- π STD
- π Hep B Positive
- π Hep B Negative
- π Hep B Unknown
- π Cocaine
- π Heroin
- π Marijuana
- π Other Drugs
- π Premature Labor
- π No Prenatal Care
- π Poor Care
- π Standard Prenatal Care

Physician/NNRL

Admission Problems *(check all applicable Reasons for Admission - see admission consult)*

Gestation

1π Preterm (<37wks)	π Term (>=37wks)	π Post-term (>42 wks)	π IUGR

Respiratory

π Apnea	π Cyanosis	π HMD
π Meconium Aspiration	π Stridor	π Respiratory Depression
π Tachypnea/Resp Distress	π Grunty	π Respiratory Depression 2nd to Maternal Narcotics

Other: _____

Cardiovascular

π Hypotension	π Cardiac Murmur	π Tachycardia
π ? Congenital Heart Defect	π ↓ Peripheral Skin Perfusion	π Bradycardia

Other: _____

Gastrointestinal

π Poor Feeding	π Abdominal Distension	π Gastroschisis
π Feeding Intolerance	π CDH	θ Omphalocele

Other: _____

Genitourinary

π Oliguria	π Congenital Renal Anomaly	π Hematuria

Other: _____

Central Nervous System

π Hypotonia	π Lethargy	π Seizures
π HIE	π Jitteriness	

Other: _____

Musculoskeletal

π Fractured Clavicle	π Talipes	π Dislocated Hip

Other: _____

Infectious Diseases

π Prolonged ROM (> 18 hr)	π Preterm ROM(< 37 wks)	π Premature ROM(prior to onset of labour)
π ? Sepsis	π Maternal Fever	π Maternal GBS

Other: _____

Fluid/Electrolytes

π Hypoglycemia(<2)	π IDM	π Acidosis	π Dehydration

Other: _____

Genetics

π Syndrome	π Other Anomalies	π Other Suspect Chromosomal Anomaly

Other: _____

Hematology

π Hyperbilirubinemia	π ABO/Rh Incompatibility	π Anemia

Other: _____

Other Reasons

π Maternal Substance Abuse	π Slow to Respond	π Meconium Staining
π Temperature Instability	π Bruising	π Difficult Delivery

Other: _____

Respiratory Form

Age at First Intubation: _____ hrs.

Initial *Arterial Only* BG: pO2 _____ pCO2 _____ pH _____

HCO3 _____ BE _____ Hgb _____ Co-ox Sat. _____%

Days of Ventilation:

HFOV	IPPV	CPAP/CYCLING ON PRONGS	NC/HOOD
/days	/days	/days	/days

Partial Days = 1 Day

Days on Oxygen

Start O_2 (y/m/d)	End/Transfer O_2 (y/m/d)

Start O_2 - date started (>.21 for 3 hours)
Stop O_2 - on .21 for > 24 hours
It doesn't matter if the baby is ventilated or not

Intubations

ETT #	2.5	3	3.5	4	Total
# of Intub.					

Interventions

Chest Tubes: Y / N
FiO2 Max (sustained >3h): _____%
Nitric Oxide: Y / N
Bronchoscopy Y / N

Surfactant Doses *(tick box after dose given)*

	First	Second	Third	Fourth	Total
Exosurf					
Survanta					
BLES					

Inhalants **Received**

Budesonide π
Beclomethasone π
Mucomyst π
Salbutamol π

NNR Lab

Polygraph (Sleep Study)

Date (y/m/d)	Result (Significant/Not)	Intervention Required
	S / N	Y / N
	S / N	Y / N
	S / N	Y / N
	S / N	Y / N
	S / N	Y / N

Central Lines

(CV = Central Venous, B = Broviac, UA = UAC, UV = UVC, PA = Peripheral Arterial)

Type	Start Date (y/m/d)	End/Transfer Date (y/m/d)

Blood Products (Hematologic Interventions) *Received* π *Not Received* π

π RBC's
π Platelets
π WBC's
π FFP
π Albumin
π Other (VZIG, factors, etc.)
π IVIG
π Cryoprecipitate

NNR LAB

GIT Interventions

Age at Start of Initial Enteral Priming (0 = day of birth) _____ days
Weight at Start of Initial Enteral Priming _____ gm

Age at Start of Initial Enteral Feeding (1 ml/kg/h) (0 = day of birth) _____ days
Weight at Start of Initial Enteral Feeding _____ gm

TPN Start Date (y/m/d)	TPN End/Transfer Date (y/m/d)

Medications: Includes drugs used only for procedures
Inhaled Drugs - see Respiratory Page

Eye Prophylaxis _____ Vitamin K _____

π AZT
π Acyclovir
π Amikacin
π Aminophylline/Theophylline
π Amoxicillin
π Amphotericin B
π Ampicillin
π Atropine
π Calcium
π Captopril
π Carbamazepine
π Cefazolin
π Cefotaxime
π Cefoxitin
π Ceftazidime
π Cephalothin
π Chloral Hydrate
π Cisapride
π Cloxacillin
π Dexamethasone
π Diazepam
π Diphenhydramine
π Digoxin
π Dopamine
π Doxapram
π Epinephrine
π Erythromycin
π Ethacrynic Acid
π Fentanyl
π Flucytosine
π Furosemide
π Gentamicin
π Hepatitis B Immunoglobulin
π Hepatitis B Vaccine
π Hyaluronidase
π Hydralazine
π Hydrochlorothiazide
π Hydrocortisone (not topical)
π Indomethacin
π Insulin
π Ketamine
π Maxeran
π Meperidine
π Metoclopramide
π Metronidazole
π Midazolam
π Morphine
π Nystatin
π Naloxone
π Nitroglycerin
π Nitroprusside
π Pancuronium
π Penicillin
π Phenobarbital
π Phenytoin
π Prostaglandin E1 (Alprostadil)
π Ranitidine
π Rifampicin
π Sodium Bicarbonate
π Sodium Polystyrene Sulfonate
π Succinycholine
π Sufentanil
π THAM
π Tobramycin
π Top. Ophthalmic
θ Trimethoprim-Sulfamethoxazole
π Trimethoprim (alone)
θ Vancomycin
π Vitamin E
π Caffeine

Other Medication/Study Drugs: _____

Discharge Information

Car Seat Evaluation: Not Done: _____ Not Necessary: _____ Transfer to Other Hospital: _____

Initial: Pass _____ Fail _____ Final: Pass _____ Fail _____

Total Number of Studies Done: _____

Home in Carbed: Y / N Home Monitor: Y / N Home on Oxygen: Y / N

Done at Discharge

Respiratory Diagnosis *Present:* π *Absent:* π

π TTN/Wet Lung
π HMD/RDS
π Meconium Aspiration Syndrome
π Pneumonia
π BPD/CLD (O2 at 28 days)
π BPD/CLD (O2 at 36 weeks)
π Apnea/Desats/Brads
π Pneumothorax
π CDH

Other: _____

Cardiovascular Diagnosis *Present:* π *Absent:* π

π Shock/Hypotension
π PPHN
π VSD
π PDA

Other: _____

Cardiovascular Interventions *Present:* π *Absent:* π

π ECG
π Echocardiogram
π Cardiac Catheterization

Central Nervous System Diagnosis *Present* π *Absent:* π

π HIE - Sarnat Stage ___
π Clinical Seizures
π ROP - Stage ___
π IVH/SEH - Papile Grade ___
π Cystic PVL
π Intraparenchymal Echodensity
π Myelomeningocele
π Ventriculomegaly post-IVH
π NAS - suspect
π NAS - definite
π NAS - req intervention

Other: _____

Central Nervous System Interventions *Present:* π *Absent:* π

π LP/Ventricular Tap
π Ultrasound
π CT
π MRI
π ABR
π VER

EEG: π Normal π Abnormal Describe: _____

Metabolic ***(indicate significant problems)*** *Present:* π *Absent:* π

Highest Lactate: _____

π Hypoglycemia (<2)
π Hyperglycemia (>12)
π Acidosis
π Hyperkalemia
π Hypocalcemia
π Hyponatremia
π Hypernatremia

Other: _____

Hematologic *Present:* π *Absent:* π

Highest Bilirubin: _____

π Phototherapy
π Exchange Transfusion
π Unconjugated Hyperbilirubinemia
π Cholestatic Jaundice
π Rh Disease
π Thrombocytopenia
π Neutropenia
π Anemia

Other: _____

Infection

Present: π *Absent:* π

θ Workup Negative

θ Significant Positive Cultures - Specify Below

A = Antepartum
I = Intrapartum
N = Nosocomial
O = Other

SITE	ORGANISM	ACQUIRED A/I/N/O
Blood		
CSF		
Urine		
Stool		
Nasopharyngeal		
ETT		
Wound		
Peritoneal		
Eye		
Umbilicus		
Abcess		

GIT Diagnosis *Present:* π *Absent:* π

π NEC: Specify: Mild Moderate Severe (circle one) π Feeding Problems π GE Reflux

Other: _____

GIT Interventions *Present:* π *Absent:* π

π EBM π Fortifier π Ultrasound
π Special Formula π Premature Formula π Contrast Radiology

Genetics/Anomalies *Present:* π *Absent:* π

π Chromosomes Pending π Chromosomes Normal

π Chromosomes Abnormal (Specify): _____
π Lethal Anomaly π FAS - definite

Other (syndrome, anomalies, etc.): _____

GU Diagnosis *Present:* π *Absent:* π

π Renal Failure Acute or Chronic π Congenital Anomaly Specify: _____

Other: _____

GU Interventions *Present:* π *Absent:* π

π Peritoneal Dialysis π Diagnostic Imaging

Surgery *Present:* π *Absent:* π

Surgery	Date (y/m/d)	UAH Y/N	Doctor	Complications

Consultant(s): _____ (Not Neonatologists) **Immunization: Y / N**

Glenrose Neonatal Follow-up Clinic: Y / N

Feeding: π **Breast** π **Formula** π **Gavage** π **TPN** π **NPO**

Metabolic Screen: ***Enter Most Recent Results***

π **Pending** π **Not Done** π **Repeat Screen Done (prematures)**

π **TSH Normal** π **Amino Acids Normal** π **Biotinidase Normal**
π **TSH Abnormal** π **Amino Acids Abnormal** π **Biotinidase Abnormal**

Comments: _____

Discharge/Transfer Medication:

π **Fer-In-Sol** π **Maxeran** π **Caffeine** π **Tri-Vi-Sol** π **Vitamin E**

Other Meds: _____

Post Mortem: Y / N

Cause of Death:

π **Respiratory Failure** π **Infection** π **Multiorgan Failure**
π **Intracranial Bleed** π **Extreme Prematurity** π **Cardiac Failure**
π **Lethal Malformation** π **Hypoxia/Ischemia** π **Withdrawal of Support**

Discharge

Discharge Date: _____ (y/m/d) **Status: Alive/Dead** **Level III Days:** _____ **Level II Days:** _____

Discharge Weight: _____ **gm.** **Head Circumference:** _____**cm** **Length:** _____**cm**

Destination: π **Normal Nursery** π **Home** π **Hospital**
π **Apprehended** π **Foster Placement**
π **Private Adoption** π **Medical Placement**

Destination Hospital: _____

Following Doctor: _____

Physician/NNRL

Appendix 2: Stollery Children's Hospital NICU datasheet

CHC NICU - ADMISSION FORM

BABY **PHN** _____

Birth Weight (gms): _____

Date of Admission (yyyy/mm/dd) ____/__/__ Admission Weight (gms) : _____

Head Circumference (cm) : _____ Length (cm) : _____ Weight Class : ❒ SGA ❒ AGA ❒ LGA

Apgars : 1 min ___ 5 min ___ 10 min ___ Gestational Age (wks) : ___

Transport : ❒ AIR ❒ LAND ❒ INBORN

Referring Physician : _____

Delivery Physician : _____

Physician : _____

Referring Hospital : _____

ADMISSION PROBLEM LIST (*check all that applies*)

❒ Lethargy *CNS*	❒ Arrhythmia	❒ Omphalocele	❒ Resp Distress *RES*
❒ Irritability	❒ Dehydration	❒ Gastroschisis	❒ Tachypnea
❒ High Pitched Cry	❒ Acidosis	❒ TEF	❒ Apnea
❒ Seizures	❒ Hypoglycemia	❒ Cleft Lip / Palate	❒ Stridor
❒ HIE	❒ IDM	❒ Imperforate Anus	❒ Cyanosis
❒ Hydrocephalus	❒ Trisomy 21 *GEN*	❒ Congenital *RENAL* Anomaly	❒ Resp Depression
❒ Meningomyelocele	❒ Syndrome	❒ Coagulopathy *HEM*	❒ HMD
❒ Other CNS Anomaly	❒ Abdominal Distension *GIT*	❒ Hyperbilirubinemia	❒ PPHN
❒ Cardiac Murmur *CVS*	❒ Feeding Intolerance	❒ ABO/Rh Incompatibility	❒ Meconium Aspiration
❒ ? Congenital Heart Defect	❒ Regurg of Bilious Material	❒ ? Sepsis	❒ Pneumonia

Other Admission Problems :

MOTHER **Name (last, first) :**

Age ___ Gravida ___ Para ___ Abort ___ Living ___ Term ___ Preterm ___ Stillbirth ___

Labour : ❒ SPONTANEOUS ❒ INDUCED ❒ NOT LABOURED	**Presentation :** ❒ VERTEX ❒ BREECH ❒ TRANSVERSE ❒ COMPOUND	**Delivery :** ❒ VAGINAL ❒ FORCEPS ❒ VACUUM ❒ C-SECTION

MATERNAL MEDICAL PROBLEM LIST (*check all that applies*)

❒ Gestational Diabetes	❒ ROM > 24 hours	❒ Tocolytic Agents
❒ Insulin Dependent	❒ Maternal Sepsis	❒ Antenatal Steroids
❒ Hypertension	❒ Oligohydramnios	❒ UTI Infection
❒ Smoker	❒ Premature Labor	❒ Multiple Birth
❒ Alcohol / Drug Abuse	❒ Placenta Previa	❒ Toxemia / Pre-eclampsia
❒ Abruptio Placentae	❒ Sexually Transmitted Diseases	❒ Maternal Fever
❒ No Prenatal Care	❒ Antibiotics	❒ Chorioamnionitis
❒ Fetal Distress	❒ Maternal Medications	❒ Maternal GBS
❒ Difficult Delivery	❒ Meconium Staining	

Other Maternal Medical Problems : **Risk Score :** ____

CHC UAH NICU - Data collection form for computer records 1

CHC NICU - CARDIOVASCULAR

Diagnosis
❒ Shock / Hypotension
❒ P. F. C.
❒ Congestive Heart Failure
❒ Arrhythmias
❒ P D A
❒ A S D
❒ V S D
❒ Coarctation
❒ Tetralogy of Fallot
❒ Transposition of Great Arteries
❒ Hypoplastic Left Heart
❒ Pulmonary Stenosis / Atresia
❒ Truncus
❒ Aortic Stenosis
❒ A-V Septal Defect
❒ Hypertension

Interventions
❒ ECG
❒ Cardiac Echo
❒ Cardiac Cath
Other CVS - Specify :

CHC NICU - CENTRAL LINES

Type	Start Date (yyyy/mm/dd)	End Date (yyyy/mm/dd)
Silastic		
Broviac		
UAC		
UVC		

CHC NICU - DIAGNOSIS / INTERVENTIONS

RESPIRATORY

- ☐ HMD
- ☐ TTN - Wet Lung
- ☐ Pulmonary Hypoplasia
- ☐ Meconium Aspiration
- ☐ Pneumonia
- ☐ Pneumothorax
- ☐ PN Mediastinum
- ☐ PIE
- ☐ Apnea
- ☐ BPD
- ☐ Pulmonary Hemorrhage
- ☐ Subglottic Stenosis
- ☐ Other Respiratory - Specify :

INFECTION

Site	*Organism* (write all that apply: GBS, Staph, Ecoli,etc.)	Antepartum / Intrapartum / Nosocomial
Blood		
CSF		
Urine		
Stool		
Nasopharyngeal		
Wound		
ETT		
Eye		

CNS *Diagnosis*

- ☐ Asphyxia
- HIE grade (1/2/3) ___
- IVH grade (1/2/3/4) ___
- Retinopathy grade (1/2/3/4) ___
- ☐ Seizures Clinical
- ☐ Seizures EEG
- ☐ Meningitis
- ☐ Myelomeningococele
- ☐ Hydrocephalus - congenital
- ☐ Ventricular Dilatation post IVH
- ☐ Periventricular Leucomalacia
- ☐ Porencephalic Cyst
- ☐ Microcephaly
- ☐ Other CNS - Specify :

GIT *Diagnosis*

- NEC : ☐ Mild ☐ Moderate ☐ Severe
- ☐ Esophageal Atresia Diag
- ☐ GE Reflux
- ☐ Imperforate Anus Diag
- ☐ Abdominal Wall Defect Diag
- ☐ Diaphragmatic Hernia Diag
- ☐ Inguinal Hernia Diag
- ☐ Meconium Ileus Diag
- ☐ Hirschprung's Disease Diag
- ☐ Small Intestinal Atresia Diag
- ☐ TE Fistule Diag
- ☐ Other GIT - Specify :

MEDICATIONS

- ☐ Digoxin
- ☐ Lasix
- ☐ Phenobarbital
- ☐ Pavulon
- ☐ Valium
- ☐ Aminophylline/Theophylline
- ☐ Doxapram
- ☐ Dopamine
- ☐ Adrenalin / Epinephrine
- ☐ Indomethacin
- ☐ OpiatesFentanyl
- ☐ Opiates Morphine
- ☐ Steroids
- ☐ Prostaglandin
- ☐ Midazolam
- ☐ Ranitidine
- ☐ Prokinetic

CNS *Interventions*

- ☐ ABR

GIT *Interventions*

- ☐ TPN

METABOLIC

- ☐ Hypoglycemia
- ☐ Hyperglycemia
- ☐ Hypocalcemia
- ☐ Hyperkalemia
- ☐ Hyponatremia
- ☐ Hypernatremia
- ☐ Rickets
- ☐ Cholestatic Jaundice
- ☐ Other Metabolic - Specify :

GENETICS

- ☐ Trisomy 13
- ☐ Trisomy 18
- ☐ Trisomy 21
- ☐ Other Chromosomal
- ☐ Multiple Anomaly non chrom Minor
- ☐ Multiple Anomaly non chrom Major
- ☐ Lethal Anomaly
- ☐ Other Congenital Anomaly - Specify :

Antibiotics

- ☐ 5 FC
- ☐ Acyclovir
- ☐ Aminoglycosides
- ☐ Amphotericin
- ☐ AZT
- ☐ Cephalosporins
- ☐ Erythromycin
- ☐ Metronidazole
- ☐ Penicilins
- ☐ Trimethoprim-Sulfamethoxazole
- ☐ Vancomycin
- ☐ Fluconazole
- ☐ Cloxacillin

HEMATOLOGIC

- Highest Bilirubin ____
- ☐ Phototherapy
- ☐ Exchange Transfusion
- ☐ Thrombocytopenia
- ☐ ABO Disease
- ☐ Rh Disease
- ☐ Neutropenia
- ☐ DIC
- ☐ Hemangioma

RENAL

- ☐ Chronic Renal Failure
- ☐ Acute Renal Failure
- ☐ Cystic Renal Malformation
- ☐ Obstructive Uropathy
- ☐ Renal Agenesis
- ☐ Renal Vascular
- ☐ Urethral Valves
- ☐ Other Renal - Specify :

☐ Other Medications - Specify

CHC NICU - SURGERY

Type	Date (yyyy/mm/dd)	Doctor
CNS		
❒ McComb Reservoir		
❒ VP Shunt		
❒ Meningomyelocele Repair		
❒ LaserTherapy		
CVS		
❒ PDA Ligation		
❒ Truncus Repair		
❒ PA Shunt		
❒ Valvuloplasty		
❒ AV Fistula Repair		
❒ Coarctation Repair		
❒ Norwood		
❒ Arterial Switch		
RENAL		
❒ UPJ Obstruction		
❒ Renal Biopsy		
❒ Hydrocele / Varicocele		
RESPIRATORY		
❒ Tracheostomy		
❒ Lobectomy		
❒ CDH		
OTHER		

Type	Date (yyyy/mm/dd)	Doctor
GIT		
❒ Bowel Resection		
❒ Colostomy		
❒ Bowel Obstruction		
❒ Inguinal Hernia Unilateral		
❒ Inguinal Hernia Bilateral		
❒ Gastroschisis		
❒ Omphalocele		
❒ Laparatomy		
❒ Closure of Ostomy		
❒ Gastrostomy Tube Insertion		
❒ Anal Sphincter Repair		
❒ TE Fistula		
❒ Esophageal Atresia		
❒ Imperforate Anus		
❒ Abdominal Wall Defect		
❒ Diaphragmatic Hernia		
❒ Meconium Ileus		
❒ Hirschprung's		
❒ Small Intestinal Atresia		

CHC NICU - DISCHARGE DATA

Discharge Status : ❒ **Alive** ❒ **Dead**

Discharge Date (yyyy/mm/dd) : ____/___/___ Weight (gms) : _____ Length (cm) : _____ Head Circum (cm) : ___

Destination :
- ❒ Home
- ❒ Hospital
- ❒ Medical Placement
- ❒ Normal Nursery
- ❒ Apprehended
- ❒ Foster Placement

Destination Hospital : _____

Following Doctor : _____
Consultant 1 : _____
Consultant 2 : _____
Consultant 3 : _____

Diagnosis

Home Medication :

❒ Home Oxygen

❒ Post Mortem

Cause of Death :
- ❒ HMD
- ❒ Intracranial Bleed
- ❒ Lethal Malformation
- ❒ Infection
- ❒ Extreme Prematurity
- ❒ Birth Asphyxia

Other Death Cause :

CHC NICU - RESPIRATORY TREATMENT

VENTILATION

IPPV	Date Start*						
	Date End*						
	Total Days						
CPAP	Date Start*						
	Date End*						
	Total Days						
HFOV	Date Start*						
	Date End*						
	Total Days						
Nitric Oxide	Date Start*						
	Date End*						
	Total Days						

AIRWAY MANAGEMENT

ETT	Size						
	Date Start*						
	Date End*						
	Total Days						

Size					
No of Intubations					

NP tube	Size						
	Date Start*						
	Date End*						
	Total Days						

SURFACTANT THERAPY

EXOSURF	Admin Date*					Doses
	Admin Time					
SURVANTA	Admin Date*					Doses
	Admin Time					
BLES	Admin Date*					Doses
	Admin Time					

☐ Chest Tubes O2 max - Specify : ____

* Enter all dates as yyyy/mm/dd

Appendix 3: Ethics Approval Forms

Health Research Ethics Board | biomedical research | health research

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University of Alberta, Edmonton, Alberta T6G 2R7
p.780.492.9734 f.780.492.7303
ethics@mecl.ualberta.ca

3-48 Corbett Hall, University of Alberta
Edmonton, Alberta T6G 2G4
p.780.492.0839 f.780.492.1626
ethics@researchplanet.ualberta.ca

ETHICS APPROVAL FORM

Date: February 2002

Name(s) of Principal Investigator(s): Dr. Joan Robinson

Department: Paediatrics

Title: Clinical characteristics and long-term neurodevelopment outcomes of meningitis in newborns with birth weight <1250 grams.

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation.

Specific Comments: This is a database review with a retrospective case control study design. No parental consent is required.

D.W. Morrish, M.D.
Chairman of Health Research Ethics Board
Biomedical Panel

This approval is valid for one year

Issue: #4091

University of Alberta | Capital Health | CARITAS HEALTH GROUP

2J2.27 Walter Mackenzie Centre
University of Alberta, Edmonton, Alberta T6G 2R7
p.780.492.9724
p.780.492.0459
f.780.492.7303
ethics@med.ualberta.ca

ETHICS APPROVAL FORM

Date: **February 2003**

Name(s) of Principal Investigator(s): **Dr. Joan Robinson**

Department: **Pediatrics**

Title: **Clinical characteristics and long-term neurodevelopmental outcomes of meningitis in newborns with birth weight < 1250 grams**

Protocol#:

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information material and consent form.

Specific Comments:

D. W. Morrish, M.D.
Chairman, Health Research Ethics Board
Biomedical Panel

This approval is valid for one year

Issue: **#4091**

University of Alberta

Capital Health

CARITAS HEALTH GROUP

Health Research Ethics Board

213 Heritage Medical Research Centre
University of Alberta, Edmonton, Alberta T6G 2S2
p.780.492.9724 (Biomedical Panel)
p.780.492.0302 (Health Panel)
p.780.492.0459
p.780.492.0839
f.780.492.7808

ETHICS APPROVAL FORM

Date: February 2005

Name(s) of Principal Investigator(s): Dr. Joan Robinson

Department: Pediatrics

Title: Clinical characteristics and long-term neurodevelopmental outcomes of meningitis in newborns with birth weight < 1250 grams

Protocol#:

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information material and consent form.

Specific Comments:

D. W. Morrish, M.D., PhD
Chairman, Health Research Ethics Board
Biomedical Panel

This approval is valid for one year

Issue: #4091

UNIVERSITY OF ALBERTA Capital Health CARITAS

Name _____ **Hospital no.** _____ **DOB** _____

Appendix 4: Case report form 1

Infants with meningitis

(Record each episode of meningitis separately if infant has meningitis on more than one occasion)

Definite meningitis Yes __

(Pure growth of a pathogen from CSF culture and increased CSF WCC with supportive clinical picture. If CSF isolate is a common skin contaminant, it must be a non-bloody tap)

Possible Yes __

(Negative CSF culture, increased CSF WCC, pretreated with antibiotics OR positive CSF culture, negative blood culture, normal CSF WCC, supportive clinical picture)

Bloody tap/contaminant Yes __

(Positive CSF culture, positive or negative blood culture, normal CSF WCC, supportive clinical picture)

Date of diagnosis of meningitis __ __ __ __/__ __/__ __
y y y y m m d d

(First day of positive CSF culture or first day of increased CSF WCC)

Postnatal age at diagnosis __ __ __ days

Postconceptional age at diagnosis __ __ weeks, __ __ days

Name _____ **Hospital no.** _____ **DOB** _____

Presenting signs and symptoms (within 48 hours of diagnosis)

(Indicate yes/no/unknown, and describe if necessary. More than one may be checked – if so, indicate which was the main symptom or most clinically significant sign or symptom)

	Yes	No	Unknown	Describe
Lethargy/ hypotonia/ decreased LOC/ other CNS				
Seizure/ suspected seizure (eg. anticonvulsants given) – see later				
Temperature instability				
Respiratory distress/ increased O2 requirements (>10% above baseline)				
Apnea/ bradycardia (new onset or increased)				
Feeding intolerance/ vomiting/ abdominal distension				
Hypotension/ tachycardia >160bpm				
Hypoglycemia < 2.5mmol/l (45g/dl)/ hyperglycemia > 10 mmol/l (180g/dl)				
Jaundice				
Other				

Name _____ **Hospital no.** _____ **DOB** _____

Seizures

(If seizures were associated or suspected with meningitis, complete the following)

		Describe
Clinical or EEG or both?	Clinical ___ EEG ___ Both ___	
Day of onset of seizures after diagnosis of meningitis	__ __ days	
Day of last recorded seizure (with reference to date of diagnosis of meningitis)	__ __ days	
Use of anticonvulsants?	Yes ___ No ___ Unknown ___	If yes, which anticonvulsants? Phenobarbitone ___ Dilantin ___ Other ___
Ongoing seizure at discharge	Yes ___ No ___ Unknown ___	
EEG done?	Yes ___ No ___ Unknown ___	Results if done:

Associated problems

	Yes	No	Unknown	Describe
Associated NEC (Bell stage II or III)				
Associated hypotension requiring inotropes				
Central line present				
Ventricular reservoir present				
Serum Na < 130mmol/l				

Name _____ **Hospital no.** _____ **DOB** _____

CSF and serum laboratory investigations

	1	2	3	4	5
Date LP done					
Age after birth (days)					
Organism(s) cultured					
Sensitive to …					
Resistant to …					
Intermediate resistance …					
CSF WCC (x 10^6/l) and differential	Total _____ N ___ (__%) L ___ (__%) M ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%)
CSF RCC (x 10^6/l)					
CSF protein (mmol/l)					
CSF glucose (mmol/l)					
CSF gram stain					
Peripheral WCC (x 10^6/l) and differential	Total _____ N ___ (__%) L ___ (__%) M ___ (__%) Baso ___ (__%) Bands ___ (__%) Other ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%) Baso ___ (__%) Bands ___ (__%) Other ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%) Baso ___ (__%) Bands ___ (__%) Other ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%) Baso ___ (__%) Bands ___ (__%) Other ___ (__%)	Total _____ N ___ (__%) L ___ (__%) M ___ (__%) Baso ___ (__%) Bands ___ (__%) Other ___ (__%)
Peripheral platelet count (x 10^9/l)					
Serum glucose (mmol/l)					

Name _____ **Hospital no.** _____ **DOB** _____

Associated infection concurrent with meningitis *(within 48 hours)*

	1	2	3	4
Date				
Age after birth (days)				
Site	Blood __ ETT __ Urine __ Other _____	Blood __ ETT __ Urine __ Other _____	Blood __ ETT __ Urine __ Other _____	Blood __ ETT __ Urine __ Other _____
Organism(s) cultured				
Sensitive to ...				
Resistant to ...				
Intermediate resistance ...				

Antibiotic use

		Duration (days)
Initial antibiotics used	Vancomycin __ Gentamicin __ Cefotaxime __ Other (specify) _____	
Specific antibiotics used	Vancomycin __ Gentamicin __ Cefotaxime __ Other (specify) _____	
Total duration of antibiotic therapy for meningitis		
Time to commencement of "appropriate" antibiotic use consistent with susceptibility patterns *(Days after first positive culture or raised CSF WCC. If antibiotic choice appropriate from start, state "zero")*		

Name _____ **Hospital no.** _____ **DOB** _____

Radiographic findings or changes after diagnosis of meningitis

	Yes	No	Date	Describe
Head ultrasound				
CT head				
MRI head				

Appendix 5: Case report form 2

CLINICAL CHARACTERISTICS AND LONG TERM NEURODEVELOPMENTAL OUTCOMES OF MENINGITIS IN PRETERM NEONATES:
Case report form of neonatal course (Cases and controls)

Demographic data

Gestational age __ __ weeks
Birth weight __ __ __ __ grams (__ __ %ile)
Sex Male __ Female __

Apgar score

1 minute		Not recorded	
5 minute		Not recorded	

Head circumference at birth __ __. __ cm

Obstetric data

Inborn __
Outborn __
If outborn, place or hospital of birth _____

Mode of delivery Vaginal __ C section __ *(tick one)*
If C section, give indication _____

Maternal risk factors:

	Yes	No	Unknown	Describe if necessary
Prolonged rupture of membranes (> 18hours)				
Chorioamnionitis *(Clinical diagnosis made by obstetrician based on uterine tenderness, foul smelling liquor, etc)*				
Maternal fever ≥38°C				
GBS positive culture				
Sepsis other than GBS				*If yes, type of organism and susceptibility patterns*
Intrapartum antibiotic use *(Within 48 hours of delivery)*				*(If yes for antibiotic use, name antibiotics used)* Penicillin __ Ampicillin __ Gentamicin __ Erythromycin __ Clindamycin __ Other _____
Antenatal steroid use *(Any antenatal steroid use at all)*				

Name _____ **Hospital no.** _____ **DOB** _____

Neonatal data

Date of discharge *(yyyy/mm/dd)* __ __ __ __/__ __/__ __
Duration of stay in NICU __ __ __ days

Neonatal course

	Yes	No	Unknown	Describe if necessary
RDS requiring surfactant therapy				Number of doses of surfactant given__ __
Inotropic support (Dopamine, Epinephrine)				
PDA				Treatment required: (*tick one or both*) Indomethacin __ Ligation __
High frequency ventilation				
Definite necrotising enterocolitis				Stage II *(Clinical picture, pneumatosis on x-ray, NPO and antibiotics)* __ Stage III *(Pneumoperitoneum, gas in portal system)* __
Chronic lung disease *(O_2 requirement >36 weeks gestation)*				
Postnatal corticosteroid use *(Any postnatal steroid use regardless of dose or duration of exposure)*				
Doxapram therapy for apnea of prematurity				

Surgical interventions

	Yes	No	Indication	Describe if necessary
PDA ligation				
Laparotomy				
Peritoneal drain				
Shunt reservoir				
VP shunt				
Inguinal hernia repair				
Tracheostomy				
Laser therapy				

Meningits and preterm infants

Name _____ **Hospital no.** _____ **DOB** _____

Sepsis *(Any infection for which the attending physician gave a full course of antibiotics)*
For infants without meningitis, any infection documented throughout NICU stay.
For infants with meningitis, sepsis related to meningitis should be filled in on the Meningitis CRF

Date	Site of infection	Organism	Antibiotics used
	Blood __ ETT __ Urine __ Other _____		Ampicillin __ Penicillin __ Cloxacillin __ Gentamicin __ Vancomycin __ Cefotaxime __ Amphotericin __ Fluconazole __ Other _____
	Blood __ ETT __ Urine __ Other _____		Ampicillin __ Penicillin __ Cloxacillin __ Gentamicin __ Vancomycin __ Cefotaxime __ Amphotericin __ Fluconazole __ Other _____
	Blood __ ETT __ Urine __ Other _____		Ampicillin __ Penicillin __ Cloxacillin __ Gentamicin __ Vancomycin __ Cefotaxime __ Amphotericin __ Fluconazole __ Other _____
	Blood __ ETT __ Urine __ Other _____		Ampicillin __ Penicillin __ Cloxacillin __ Gentamicin __ Vancomycin __ Cefotaxime __ Amphotericin __ Fluconazole __ Other _____

Highest grade IVH __
Describe:

_____
_____
_____

Presence of periventricular leukomalacia Yes __ No __
Describe:

_____
_____
_____

Highest stage ROP: __

Head circumference at discharge: __ __. __ cm

Name _____ **Hospital no.** _____ **DOB** _____

Neonatal outcomes

ABR prior to discharge from NICU
Done? Yes __ No __
Normal? Yes __ No __
If abnormal, describe:

_____

_____

Death in NICU Yes __ No __
If yes, age at death __ __ __ days
Most likely cause of death *(tick applicable causes):*

Respiratory failure	
Intracranial bleed	
Lethal malformation	
Infection	
Extreme prematurity	
Hypoxia/ischemia	
Multiorgan failure	
Cardiac failure	
Withdrawal of support	
Other	